OEI-10014

Center for Regulatory Effectiveness C4-001

Suite 700
11 Dupont Circle, N.W.
Washington, D.C. 20036
Tel: (202) 265-2383 Fax: (202) 939-6969
www.TheCRE.com

May 31, 2002

Docket ID No. OEI-10014
United States Environmental Protection Agency
Northeast Mall
Room B607
401 M St. SW
Washington, D.C. 20460

RE: CRE Comments on Proposed Data Quality Guidelines

Dear Sir or Madam:

I am writing on behalf of the Center for Regulatory Effectiveness (CRE) to share with you the Center's comments on your agency's recently proposed information quality guidelines, issued pursuant to the Data Quality Act (44 U.S.C. § 3516, note). As you may be aware, the Center had a leading role in passage of the Act and maintains a strong ongoing interest in this important issue. I invite you to visit the CRE website (www.TheCRE.com) for further details.

In light of the deference the public pays to governmental information and its significant role in regulation and resource allocation in both the public and private sectors, the quality of the federal government's information is a matter of critical importance. Consequently, CRE appreciates this opportunity to provide its views and recommendations to the agency in order to achieve the intent of Congress in enacting this new "Good Government" law and of OMB in promulgating its guidelines containing government-wide Data Quality standards (67 *Fed. Reg.* 8452, Feb. 22, 2002).

To assist the agency in meeting its obligations under the Data Quality Act and OMB's guidelines, CRE has prepared and enclosed the following attachments:

(1) **CRE General Comments to All Federal Agencies Related to Data Quality Guidelines**
- This paper outlines a number of cross-cutting issues related to Data Quality guidelines which are applicable to all agencies and contains CRE's recommendations on how such issues should be addressed.

- CRE strongly believes that proper action on these key issues will help ensure that the guidelines issued by the agency are workable, effective, and in keeping with the requirements of both the statute and the government-wide standards set by OMB.

- In the paper, CRE identifies and evaluates a number of agency approaches to these cross-cutting issues. Such examples include positive agency proposals which might be emulated, as well as problematic agency proposals which should be avoided.

(2) Legal Memorandum on the Data Quality Act's Applicability to All Public Information

- CRE has been troubled by several agencies' attempts in their proposed guidelines to exempt certain categories of public information from the Data Quality Act's standards. Consequently, CRE retained Multinational Legal Services (MLS) to examine this important issue. Attached is a legal memorandum which summarizes the MLS inquiry into the Data Quality Act's applicability to all public information. In short, MLS found:

  - Analysis of the Data Quality Act, the Public Information provisions of the Paperwork Reduction Act, and legislative history demonstrate that Congress intended Data Quality Act standards to apply to <u>all</u> public information.

  - Thus, neither OMB nor any other federal agency has discretion to violate this legislative intent by exempting categories of information from the standards set forth pursuant to the Data Quality Act.

(3) CRE's Specific Comments On EPA's Proposed Data Quality Guidelines

Finally, CRE believes that in light of the ongoing importance of the Data Quality issue, all federal agencies should adopt Data Quality as a Performance Goal in its Performance Plan under the Government Performance and Results Act. Not only would this assist the agency in regularly monitoring and improving its information quality activities, but it would also serve to increase the transparency of the agency process for Congress and the interested public.

CRE would be happy to answer any questions you might have related to its comments and supporting materials. Please contact us at (202) 265-2383, if we might be of further assistance.

Sincerely,

Jim J. Tozzi
Member, CRE Board of Advisors

CENTER FOR REGULATORY EFFECTIVENESS'S INITIAL COMMENTS ON EPA'S PROPOSED DATA QUALITY GUIDELINES DOCKET OEI-10014

The Center for Regulatory Effectiveness ("CRE") submits the following comments on the United States Environmental Protection Agency's proposed data quality guidelines, 67 FR 21234 (April 30, 2002).

In addition to these EPA-specific comments, we are attaching as Exhibit A CRE's Generic Comments to all Federal Agencies Related to Data Quality Guidelines ("CRE Generic Comments"). CRE's Generic comments are incorporated by reference into CRE's comments on EPA's proposed data quality guidelines. CRE's Generic Comments, while not limited to EPA, address several issues presented by EPA's proposed guidelines.

While CRE has comments on several specific aspects of EPA's proposed guidelines, we wish to emphasize one general comment on the guidelines.

EPA Cannot Exempt Publicly Disclosed Information From the Data Quality Guidelines

EPA's proposed data quality guidelines violate clear congressional intent that they must apply to all information that EPA has in fact made public. Rather than complying with the statutory mandate, EPA proposes to exempt much of the Agency's public information from coverage by the guidelines. *E.g.*,

- Proposed Guidelines, pages 14-17(exemptions from the definitions of dissemination and information)

- Proposed Guidelines, page 23 (exempting rulemakings from the guidelines' administrative correction process).

- Proposed Guidelines, page 16 (exempting information distribution related to adjudicative processes, with "adjudicative processes" defined extremely broadly)

EPA's proposed data quality guidelines are required by the Information Dissemination provisions of the PRA. 44 U.S.C. §§ 3504(d)(1); 3516 note; 66 FR 49718 (Sept. 28, 2001). Attached as Exhibit B is a legal memorandum prepared by Multinational Legal Services, PLLC, for CRE. This memorandum is incorporated by reference into CRE's comments on EPA's proposed data quality guidelines. This memorandum examines the relevant statutory text and legislative history, and concludes that neither the Office of Management and Budget ("OMB") nor any other federal agency has any authority or discretion to exempt any publicly disclosed information from coverage by the data quality guidelines required by the Information Dissemination provisions of the Paperwork Reduction Act.

EPA's proposed data quality guidelines are also inconsistent with the definition of "information" in OMB Circular A-130, which defines the term at page 3 to mean "any

communication or representation of knowledge such as facts, data, or opinions in any medium or form, including textual, numerical, graphic, cartographic, narrative, or audiovisual forms." There is no rational basis for using a different, conflicting definition of "information" for the data quality guidelines required by the PRA's Information Dissemination requirements. OMB Circular A-130 is issued pursuant to the PRA's Information Dissemination requirements and eight other federal statutes, as well as three Executive Orders. Consistent with congressional intent, OMB's Circular A-130 Information dissemination definition of "information" is much broader than OMB's definition of "information" for purposes of the PRA's separate Collection of Information requirements. *Compare* OMB Circular A-130, at 3 *with* 5 CFR 1320.3(h)(OMB's definition of "information" for PRA Collections of Information).

In regard to this issue, CRE further incorporates by reference Exhibit A to CRE's comments, including but not limited to pages 2-10; and Exhibit B to CRE's comments.

Consequently, CRE requests EPA to revise its proposed data quality guidelines to state explicitly that they apply to any and all information that EPA in fact makes public.

EPA Cannot Exclude Rulemakings and Adjudicative Processes From the Data quality Standards and Petition Process

EPA's proposed guidelines, at pages 22-23, appear to exclude most rulemaking records from the Data Quality Act petition and correction process:

> ... where a mechanism by which to submit comments to the Agency is already provided. For example, EPA rulemakings include a comprehensive public comment process and impose a legal obligation on EPA to respond to comments on all aspects of the action. These procedural safeguards assure a thorough response to comments on quality of information. EPA believes that the thorough consideration required by this process meets the needs for the correction of information process. A separate process for information that is already subject to such a public comment process would be duplicative, burdensome, and disruptive to the orderly conduct of the action.
>
> If EPA cannot respond to a complaint in the response to comments for the action (for example, because the complaint is submitted too late to be considered along with other comments or because the complaint is not germane to the action), EPA will consider whether a separate response to the complaint is appropriate. EPA may consider frivolous any complaint which could have been submitted as a timely comment in the rulemaking or other action but was submitted after the comment period.

These proposed exclusions could, as a practical matter, remove all EPA rulemaking records from coverage under the Data Quality Act. This exclusion is contrary to the letter and intent of the Act, as explained in Exhibit B to these comments, which is incorporated herein by reference.

Moreover, many rulemakings are very lengthy proceedings. Information in a rulemaking public docket may be publicly available for years before the agency takes any action on comments on the information in its proposed rules and docket. Not allowing a Data Quality guidelines petition to correct this information before promulgation of final rules would violate OMB's interagency Data Quality guidelines, which require a timely correction process for correcting errors in all agency information made publicly available, including "preliminary information" used in agency rulemakings:

> ... agencies shall establish administrative mechanisms allowing affected persons to seek and obtain, where appropriate, *timely correction of information* maintained and disseminated by the agency that does not comply with OMB or agency guidelines. These administrative mechanisms shall be flexible, *appropriate to the nature and timeliness of the disseminated information*, and incorporated into agency information resources management and administrative practices.
>
> i. *Agencies shall specify appropriate time periods* for agency decisions on whether and how to correct the information, and agencies shall notify the affected persons of the corrections made.
>
> ii. If the person who requested the correction does not agree with the agency's decision (including the corrective action, if any), the person may file for reconsideration within the agency. The agency shall establish an administrative appeal process to review the agency's initial decision, *and specify appropriate time limits* in which to resolve such requests for reconsideration.

67 FR 8452, 8459 (Feb. 22, 2002)(emphasis added).

> OMB does not believe that an exclusion for preliminary information is necessary and appropriate. It is still important that the quality of preliminary information be ensured and that preliminary information be subject to the administrative complaint-and-correction process.

Similarly, EPA's definition of "dissemination" at page 16 excludes publicly disclosed information "related" to "adjudicative processes." EPA's definition of "adjudicative processes" at pages 16-17 is so broad that it includes most EPA information that is not included within EPA's rulemaking exemption. These two exemptions, when combined with the other proposed

exemptions, exclude from the data quality guidelines most information that EPA makes public.

CRE's legal memorandum attached as Exhibit B to these comments explains that these exemptions from the data quality standards are not permitted under the Data Quality Act amendments to the Information Dissemination requirements of the Paperwork Reduction Act.

Application of the SDWA Health Risk Assessment Standards

EPA's proposed guidelines at page 9 state that EPA will only adapt the SDWA risk assessment standards, without explaining how or why. Moreover, EPA proposes to defer any action regarding the SDWA standards for environmental and safety risk assessments, without explaining why.

OMB's February 22nd agency-wide guidelines stated that the science quality and risk assessment standards contained in the 1996 amendments to the Safe Drinking Water Act (SDWA), 42 U.S.C. § 300g-1(b)(3)(B), should be adopted or adapted by federal agencies. Agencies should adopt both the SDWA science quality and risk assessment standards unless they conflict with the other federal statutory requirements. If such conflicts do arise, agencies should make every efforts to reconcile the SDWA standards with the conflicting statutory requirements.

There are only two valid reasons why a federal agency should not adopt these standards:

- The agency does not conduct these types of risk assessments; or
- The SDWA risk assessment standards conflict with the specific risk assessment standards of another federal statute governing the agency.

In the latter case, the agency should identify the conflicting specific risk assessment standards; make every effort to reconcile the conflicting standards with the SDWA standards; and request public comment on both the conflict and the attempt at reconciliation.

The SDWA risk assessment standards, and compliance with other data quality standards (e.g., quality, objectivity and utility) are especially critical for EPA environmental risk assessment standards. EPA's own SAP and virtually every one else who has reviewed the Agency's practice in this area agree that EPA's current environmental risk assessments do not meet Data Quality Act standards in large part because EPA does not use probabilistic risk assessments.

For example, EPA's Office of Pesticide Programs explains on its website (emphasis added):

> In May 1996 the Environmental Fate and Effects Division (EFED) of the Office of Pesticide programs (OPP) presented two pesticide risk assessment case studies to EPA's Scientific Advisory Panel (SAP) and asked them to address the agency's current pesticide

> risk assessment methodology. *The SAP commented that while the current process is believed to be cautious and protective in terms of adverse environmental effects, it best serves as a screen because it provides little information on the likelihood of damage. The SAP recommended that the pesticide risk assessment process be expanded to include probabilistic assessments of risk and to identify the uncertainties associated with the assessment.*

EPA's Ecological Committee on FIFRA Risk Assessment Methods ("ECOFRAM") published in 1999 an Aquatic Report which on page 3 summarized the SAP's conclusions in part as follows (emphasis added):

> The panel suggested that the current test methodologies and specific endpoints used by OPP in its model assessments were designed to support the relatively simplistic process of hazard assessment, not risk assessment. The Panel indicated that the current approach has a number of limitations, *and its utility in risk assessments is of questionable value.* They also pointed out that gaps in the current methodologies must be filled to accomplish effective and comprehensive risk assessments. *As a result, they strongly urged OPP EFED to conduct probabilistic assessments (risk assessments) to evaluate the ecological impacts from pesticides.*

In sum, the type of lower-tier analyses used by EPA for environmental risk assessments have been subject to formal, independent, external peer review and found lacking in this context. By contrast, a probabilistic risk assessment is the type of analysis found necessary by formal, independent, external peer review.

The PRA Data Quality guidelines require that all information disseminated by EPA to the public have "utility." The OMB definition of "utility" explains that this term "refers to the usefulness of the information to its intended users, including the public." As noted above, EPA's own SAP emphasized that the type of lower-tier analyses used by EPA, instead of a probabilistic risk assessment, has "utility...of questionable value." EPA's own SAP urged the Agency "to conduct probabilistic assessments (risk assessments) to evaluate the ecological impacts from pesticides." The SAP further cautioned that the lower-tier analysis "best serves as a screen because it provides little information on the likelihood of damage." In fact, as the SAP pointed out, this type of lower-tier analysis "is designed to support the relatively simplistic process of hazard assessment, not risk assessment." EPA itself admits that its lower-tier analysis does "not imply any quantification of magnitude or probability of effect." Yet EPA still relies on this type of risk assessment to determine environmental risks.

OMB's Guidelines also require "objectivity" in information EPA disseminates to the public. The OMB definition of "objectivity" explains (emphasis added), "In a scientific or statistical context, the original or supporting data shall be generated, and the analytical results shall be developed, *using sound statistical and research methods.*" 67 FR 8452, 8459 (Feb. 22, 2002).

EPA's SAP has concluded that the type of lower-tier analysis used by EPA is not a sound

statistical and research method for ecological risk assessments. In fact it is only a hazard assessment, not a full-fledged risk assessment. Probabilistic risk assessments are the sound statistical and research method in this context.

There other examples of EPA risk assessment practices that are inconsistent with the SDWA risk assessment standards and other data quality standards. One of these is EPA's categorical prohibition on the consideration of third party clinical human test data pending NAS review of these types of tests. Attached as Exhibit C to CRE's comments is a Petition CRE filed with EPA on this issue. This CRE petition is incorporated by reference into CRE's comments on EPA's Data Quality Guidelines.

CRE's Petition explains that third party clinical human test data are among the best available data regarding any substance or product's risk to human health. EPA's categorical ban on consideration and use of such data violates the SDWA risk assessment standards and other Data Quality requirements: *e.g.*, objectivity, utility and quality.

CRE hopes that EPA's decision regarding adoption and use of the SDWA risk assessment standards is not influenced by whatever concerns motivated its categorical ban on third party clinical human test data. In any event, EPA cannot promulgate final data quality guidelines that comply with the required data quality standards while still maintaining its categorical ban on use and consideration of third party clinical human test data.

Reproducibility Of Original Data

EPA's proposed Data Quality Act guidelines at page 8 recognize the importance of reproducibility as a fundamental test of science: "As a regulatory agency with a strong science program and function, EPA takes reproducibility of data and results very seriously and understands the importance of ensuring that data and methods are transparent and credible."

EPA's proposed Data Quality Act Guidelines request public comment on a number of reproducibility issues, including the following at page 25: "What types of original and supporting data do you believe should or should not be subject to a reproducibility requirement given ethical, feasibility, or confidentiality constraints?"

In response to this question, the original and supporting data for all laboratory animal studies should be capable of being reproduced. EPA relies heavily on animal studies in many of its regulatory contexts, and animal studies are often the primary basis for EPA regulatory action. The original and supporting data from these animal tests are often the most influential data used by EPA in regulating. Consequently, EPA's guidelines should be revised to state that if a qualified laboratory using the same test protocols achieves significantly different results in regard to the data generated by the original test, then EPA will assume that the original test does not meet data quality standards. CRE believes that requirement could be implemented, and the original test shown invalid, primarily through third party administrative petitions. If the information in question has to be part of a public record under the APA or some other law or

regulation, then any correction petition, EPA action on it, and the results of any judicial review of the petition, should all be in the public record. There are no ethical or feasibility obstacles to such a requirement. Confidentiality issues are discussed in CRE's Generic Comments at pages 23-25.

CRE also comments that any animal test results that cannot be reproduced do not meet the required data quality standards of objectivity, quality, and utility. Consequently any such test should be subject to an administrative correction petition on these grounds.

Retroactive Application of the Data Quality Guidelines

In regard to this issue, CRE incorporates by reference Exhibit A to CRE's comments, including but not limited to page 5; and Exhibit B to CRE's Comments.

Third-Party Submissions of Data to An Agency

In regard to this issue, CRE incorporates by reference Exhibit A to CRE's comments, including but not limited to page 10; and Exhibit B to CRE's Comments.

Definition of "Affected Persons"/Definition of a "Person"

In regard to this issue, CRE incorporates by reference Exhibit A to CRE's comments, including but not limited to page 10; and Exhibit B to CRE's Comments.

Deadline for Deciding a Petition

In regard to this issue, CRE incorporates by reference Exhibit A to CRE's comments, including but not limited to page 13; and Exhibit B to CRE's Comments.

Who Decides the Initial Petition?

In regard to this issue, CRE incorporates by reference Exhibit A to CRE's comments, including but not limited to page 14; and Exhibit B to CRE's Comments.

Who Decides Appeals?

In regard to this issue, CRE incorporates by reference Exhibit A to CRE's comments, including but not limited to page 15; and Exhibit B to CRE's Comments.

Must the Agency Correct Information When It Agrees with a Petition?

In regard to this issue, CRE incorporates by reference Exhibit A to CRE's comments, including but not limited to page 16; and Exhibit B to CRE's Comments.

What is the Standard for Rebutting the Presumption of Objectivity Resulting from Peer Review?

In regard to this issue, CRE incorporates by reference Exhibit A to CRE's comments, including but not limited to page 17; and Exhibit B to CRE's Comments.

How is "Influential Information" Defined?

In regard to this issue, CRE incorporates by reference Exhibit A to CRE's comments, including but not limited to pages 18-19; and Exhibit B to CRE's Comments.

What is "Objective" and "Unbiased" Information on Risks to Human Health, Safety and the Environment?

In regard to this issue, CRE incorporates by reference Exhibit A to CRE's comments, including but not limited to pages 20-22; and Exhibit B to CRE's Comments.

Robustness Checks for CBI

In regard to this issue, CRE incorporates by reference Exhibit A to CRE's comments, including but not limited to page 23; and Exhibit B to CRE's Comments.

Use of Third-Party Proprietary Models

In regard to this issue, CRE incorporates by reference Exhibit A to CRE's comments, including but not limited to pages 24-25; and Exhibit B to CRE's Comments.

CRE GENERIC COMMENTS TO ALL FEDERAL AGENCIES RELATED TO DATA QUALITY GUIDELINES

Introduction

OMB's Data Quality guidelines have provided a strong foundation for improvement in the overall quality of information which the federal government disseminates to the public. However, as acknowledged by Congress in passage of the Data Quality Act, individual agencies must promulgate their own conforming Data Quality guidelines that address the unique characteristics and information products of their programs. It is imperative that these agency guidelines be drafted in such a way as to ensure that they are workable, effective, and in keeping with the government-wide standards set by OMB.

To assist in this process, the Center for Regulatory Effectiveness (CRE) has compiled a list of key issues related to the Data Quality guidelines and reviewed a large number of agency guidelines issued to date to see if and how these important topics have been addressed. CRE sees these as "cross-cutting" issues, in that they would apply to most if not all federal agencies. The balance of the paper will provide:

- Statement of the cross-cutting issue.
- Explanation of the issue, its importance, and CRE's recommended approach.
- Examples of current agency proposals on the issue which are satisfactory (if any) and the reasoning for that conclusion.
- Examples of current agency proposals on the issue which are unsatisfactory (if any) and the reasoning for that conclusion.

CROSS-CUTTING ISSUES RELATED TO AGENCY DATA QUALITY GUIDELINES

(1) Exemptions from Applicability of the Data Quality Guidelines

OMB's interagency Data Quality guidelines exempt some types and categories of information the Data Quality guidelines. Many other agencies have proposed additional exemptions. *As demonstrated in the accompanying Legal Memorandum, the OMB and additional agency exemptions from the Data Quality guidelines contradict clear congressional intent to the extent that they exempt any information that an agency has in fact made public. Neither OMB nor any other federal agency has authority to make such exemptions.*

OMB's interagency Data Quality guidelines exempt from their coverage certain publicly disclosed federal agency information:

> "Dissemination" means agency initiated or sponsored distribution of information to the public (see 5 CFR 1320.3(d) (definition of "Conduct or Sponsor")). Dissemination does not include distribution limited to government employees or agency contractors or grantees; intra- or interagency use or sharing of government information; and responses to requests for agency records under the Freedom of Information Act, the Privacy Act, the Federal Advisory Committee Act or other similar law. This definition also does not include distribution limited to correspondence with individuals or persons, press releases, archival records, public filings, subpoenas or adjudicative processes.

67 FR 8452, 8460 (Feb. 22, 2002).

This definition of "dissemination" is considerably narrower than OMB's previous definitions of this term in a PRA context. For example, in OMB Circular A-130, at page 3 OMB defined "dissemination" to mean:

> ... the government initiated distribution of information to the public. Not considered dissemination within the meaning of this Circular is distribution limited to government employees or agency contractors or grantees, intra-or-inter-agency use or sharing of government information, and responses to requests for agency records under the Freedom of Information Act (5 U.S.C. 552) or Privacy Act."

Other agencies have included the OMB exemptions in their proposed Data Quality guidelines. Some agencies have proposed to expand the OMB exemptions, or to add new exemptions. For example:

Retroactivity Exemption (See Issue #2)

Several agencies, such as NIH at page 4 of its guidelines, make statements indicating that their guidelines, and the OMB guidelines, will apply only to information that is initially disseminated initially after October 1, 2002. This proposed exemption contradicts OMB's interagency guidelines which specify that they apply to information created or originally disseminated prior to October 1, 2002, if an agency continues to disseminate the information after that date.

Case-by-Case Exemption (See Issue #3)

Several agencies, including EPA at pages 22-23 of its proposed guidelines, propose application of the PRA's Data Quality guidelines on a case-by-case basis, rather than application of them to all information disseminated by the agency.

Rulemaking Exemption (See Issue #4)

A number of agencies, including EPA at page 22-23 and the Department of the Treasury at page 6 of their proposed guidelines, have stated that the Data Quality error correction process required by OMB's interagency Data Quality guidelines will not apply to information in proposed rulemakings, and that any alleged errors will be addressed only through the rulemaking notice and comment process. It is not clear from these proposed exemptions whether the agencies believe that any of the PRA's Data Quality standards apply to information disseminated during rulemakings.

Adjudicative Processes Exemption

EPA's proposed data quality guidelines, at page 17, substantially expand OMB's adjudicative processes exception by broadening it to include, *inter alia*:

> Distribution of information in documents relating to any formal or informal administrative action determining the rights and liabilities of specific parties, including documents that provide the findings, determinations or basis for such actions. Examples include the processing or adjudication or applications for a permit, license, registration, waiver, exemption, or claim; actions to determine the liability of parties under applicable statutes and regulations; and determination and implementation of remedies to address such liability.

The OMB interagency and individual agency Data Quality guidelines are promulgated under and implement the Information Dissemination requirements of the Paperwork Reduction Act ("PRA"). 44 U.S.C. §§ 3504(d)(1), 3516 note. The Multinational Legal Services (MLS) Legal Memorandum accompanying CRE's Generic Data Quality Comments explains that the relevant statutory text and legislative history demonstrate clear congressional intent that these Data Quality guidelines, like the PRA's other Information Dissemination requirements, apply to any and all information that federal agencies have in fact made public. By contrast to the PRA's separate Collection of Information requirements, there are no statutory exemptions from any of the PRA's Information Dissemination requirements. OMB's attempt to create exemptions by restricting the definition of "dissemination" in its interagency Data Quality guidelines contradicts Congress' own pervasive and all encompassing use of this term. OMB's "dissemination" exemptions in its interagency Data Quality guidelines are also inconsistent with OMB's prior, much broader definition of "dissemination" in implementing the PRA's Information Dissemination requirements. The additional exemptions proposed by other federal agencies also violate clear congressional intent because OMB cannot provide any exemptions from its interagency Data Quality guidelines, and the other agencies have to comply with OMB"s interagency guidelines. 44 U.S.C. §§ 3504(d)(1); 3506(a)(1)(B); 3516 note.

(2) Retroactive Application of the Data Quality Guidelines

In compliance with the statute, each agency's Data Quality guidelines must become effective on October 1, 2002. The guidelines must apply to information being disseminated on or after October 1, regardless of when the information was first disseminated. This retroactivity principle is explicitly enunciated in OMB's February 22, 2002 guidelines, at III.4. All agency guidelines are required to comply with the requirements set forth by OMB in their interagency February 22nd Final Guidelines. 44 U.S.C. §§ 3504(d)(1); 3506(a)(1)(B); 3516 note.

Example(s) of Satisfactory Agency Proposals

Department of Justice

DOJ's draft guidelines state at page 2, "These guidelines will cover information disseminated on or after October 1, 2002, regardless of when the information was first disseminated...."

These guidelines are in full compliance with the retroactivity provision in OMB's February 22nd guidelines.

Example(s) of Unsatisfactory Agency Proposals

National Institutes of Health

The NIH guidelines state at p.4, "The OMB guidelines apply to official information (with the NIH imprimatur) that is released on or after October 1, 2002."

NIH's statement about OMB's guidelines directly contradicts the text of OMB's guidelines which clearly state that they "shall apply to information that the agency disseminates on or after October 1, 2002, regardless of when the agency first disseminated the information." [Emphasis added]

(3) Individual Agency Guidelines Must Comply with OMB's Interagency Guidelines; and There Are No Case-By-Case Exemptions From Applicability Of The Guidelines

OMB's interagency Data Quality guidelines implement section 3504(d)(1) of the PRA. 44 U.S.C. § 3516 note. Section 3504 \(d)(1) requires that "with respect to information dissemination, the [OMB] director shall develop and oversee the implementation of policies, principles, standards, and guidelines to apply to Federal agency dissemination of public information, regardless of the form or format in which such information is disseminated...." 44 U.S.C. § 3504(d)(1). All federal agencies subject to the PRA must comply with OMB's interagency Data Quality guidelines when they issue their own Data Quality guidelines. 44 U.S.C. §§ 3504(d)(1); 3506(a)(1)(B); 3516 note. The MLS Legal Memorandum accompanying CRE's Generic Data Quality Guidelines explains that Congress clearly intended OMB's Data Quality guidelines to apply to all information agencies subject to the PRA in fact make public

Example(s) of Satisfactory Agency Proposals

None

All agency guidelines reviewed appear to try to reduce significantly the binding nature indicated in the OMB guidelines.

Example(s) of Unsatisfactory Agency Proposals

Multiple Agencies

None of the agency proposals reviewed make any reference to the directives of the PRA; they refer only to section 515 of the FY 2001 Consolidated Appropriations Act, the Data Quality Act itself, and ignore the fact that the Data Quality Act expressly states that the Data Quality guidelines are promulgated under and implement the PRA.

EPA's proposal states that its guidelines do not impose any "legally binding requirements or obligations.... The guidelines may not apply to a particular situation based on the circumstances, and EPA retains discretion to adopt approaches on a case-by-case basis that differ from the guidelines, where appropriate." Sec. 1.1. "Factors such as imminent threats to public health or homeland security, statutory or court-ordered deadlines, or other time constraints, may limit or preclude applicability of these guidelines." Sec. 1.2. Information that generally would not be covered by the guidelines includes "information in press releases and similar announcements: These guidelines do not apply to press releases, fact sheets, press conferences or similar communications in any medium that announce, support the announcement or give pubic notice of information EPA has disseminated elsewhere." Sec. 1.3, Ins. 482-85.

The CDC/ATSDR proposal has lists of information products to which the guidelines do and do not apply. It also includes press releases and interviews, but does not include "similar announcements," as does EPA. The umbrella HHS guidelines state that the quality standards do not apply to press releases. Sec. D.3.

The NIH proposal also lists with considerable specificity types of information covered and not covered. Press releases are listed as not covered. There is no qualification as to whether a press release simply announces, supports an announcement, or gives public notice of information the agency has disseminated elsewhere, as in EPA's proposal. Sec. II, 2. The NIH proposal states that its information dissemination products must conform to the OMB guidelines. Sec. V, 1.

DOT's proposal states that it contains only "suggestions, recommendations, and policy views of DOT. They are not intended to be, and should not be construed as, legally binding requirements or mandates. These guidelines are intended only to improve the internal management of DOT . . . ." Sec. III, b. The DOT proposal is very specific in excluding certain types of information. Information presented to Congress is excluded if it is "not simultaneously disseminated to the public". III, j. Also excluded are "[p]ress releases and other information of an ephemeral nature, advising the public of an event or activity of a finite duration - regardless of medium". III, k.

The DOL proposal begins with a Preface which states that the document provides an "overview" of the agency's "efforts" to ensure and maximize information quality. DOL states that the guidelines are only intended to improve the internal management of the government and "are not intended to impose any binding requirements or obligations on the Department . . . A Departmental agency may vary the application of information quality guidelines in particular situations where it believes that other approaches will more appropriately carry out the purpose of these guidelines or will help an agency to meet its statutory or program obligations." DOL also specifies certain types of information to which the guidelines do not apply, including press releases, adjudicative processes, policy guidance, and statements of legal policy or interpretation. Sec. on "Scope and Applicability".

The CPSC proposal states that information is not subject to the guidelines if it states explicitly that it was not subjected to them. P.5.

Finally, all of the above agency proposals exempt material relating or adjudicatory proceedings or processes, including briefs and other information submitted to courts. *See e.g.*, DOT at IV, g.

(4) Inclusion of Rulemaking Information in the Data Quality Act Petition Process

Information present in rulemaking records, both completed and ongoing, comprises much of the information disseminated by federal agencies. Neither the Data Quality Act itself nor OMB's February 22nd agency-wide guidelines exclude rulemaking records from coverage.

Example(s) of Satisfactory Agency Proposals

None

Example(s) of Unsatisfactory Agency Proposals

EPA; Treasury

EPA's proposed guidelines, at pages 22-23, appear to exclude most rulemaking records from the Data Quality Act petition and correction process:

> ... where a mechanism by which to submit comments to the Agency is already provided. For example, EPA rulemakings include a comprehensive public comment process and impose a legal obligation on EPA to respond to comments on all aspects of the action. These procedural safeguards assure a thorough response to comments on quality of information. EPA believes that the thorough consideration required by this process meets the needs for the correction of information process. A separate process for information that is already subject to such a public comment process would be duplicative, burdensome, and disruptive to the orderly conduct of the action.
>
> If EPA cannot respond to a complaint in the response to comments for the action (for example, because the complaint is submitted too late to be considered along with other comments or because the complaint is not germane to the action), EPA will consider whether a separate response to the complaint is appropriate. EPA may consider frivolous any complaint which could have been submitted as a timely comment in the rulemaking or other action but was submitted after the comment period.

The Treasury Department's proposed guidelines (page 5) also have a rulemaking exclusion.

These proposed exclusions could, as a practical matter, remove all EPA and Treasury rulemaking records from coverage under the Data Quality Act. This exclusion is contrary to the letter and intent of the Act, as explained in the MLS Legal memorandum accompanying CRE's Generic Data Quality Guideline comments.

Moreover, many rulemakings are very lengthy proceedings. Information in a rulemaking public docket may be publicly available for years before the agency takes any action on comments on the information in its promulgation of final rules. Not allowing a Data Quality guidelines petition to correct this information before promulgation of final rules would violate OMB's interagency Data Quality guidelines, which require a timely correction process for correcting errors in all agency information made publicly available, including "preliminary information" used in agency rulemakings:

> ... agencies shall establish administrative mechanisms allowing affected persons to seek and obtain, where appropriate, *timely correction of information* maintained and disseminated by the agency that does not comply with OMB or agency guidelines. These administrative mechanisms shall be flexible, *appropriate to the nature and timeliness of the disseminated information*, and incorporated into agency information resources management and administrative practices.
>
> i. *Agencies shall specify appropriate time periods* for agency decisions on whether and how to correct the information, and agencies shall notify the affected persons of the corrections made.
>
> ii. If the person who requested the correction does not agree with the agency's decision (including the corrective action, if any), the person may file for reconsideration within the agency. The agency shall establish an administrative appeal process to review the agency's initial decision, *and specify appropriate time limits* in which to resolve such requests for reconsideration.

67 FR 8452, 8459 (Feb. 22, 2002)(emphasis added).

> OMB does not believe that an exclusion for preliminary information is necessary and appropriate. It is still important that the quality of preliminary information be ensured and that preliminary information be subject to the administrative complaint-and-correction process.

66 FR 49718, 49720 (Sept. 28, 2001).

(5) Third-Party Submissions of Data to An Agency

Much of the information disseminated by federal agencies is originally submitted by states or private entities. In addition, federal agencies often disseminate research from outside parties, some of which is funded by the agency.

The MLS Legal Memorandum accompanying CRE's Generic Data Quality Comments explains that Congress clearly intended the Data Quality guidelines to apply to all information that agencies in fact make public. Consequently, all third-party information that an agency makes public is subject to the Data Quality guidelines.

Where an agency does not use, rely on, or endorse third-party information, but instead just makes it public, then the agency itself should have not have the initial burden of ensuring that the information meets the quality, objectivity, utility and integrity standards required by the Data Quality guidelines. The information should, however, be subject to the Data Quality correction process through administrative petitions by third parties.

When, however, an agency uses, relies on, or endorses third-party information, then the agency itself should have the burden of ensuring that the information meets the quality, objectivity, utility, and integrity standards required by the Data Quality guidelines.

Example(s) of Satisfactory Agency Proposals

Department of Transportation

While not entirely consistent with the PRA's Data Quality requirements, the Department of Transportation at page 8 of its proposal guidelines comes close to meeting these requirements:

> The standards of these guidelines apply not only to information that DOT generates, but also to information that other parties provide to DOT, if the other parties seek to have the Department rely on or disseminate this information or the Department decides to do so.

Example(s) of Unsatisfactory Agency Proposals

CPSC; EPA

The Consumer Product Safety Commission on page 3 of its proposed guidelines stated that "the standards and policies applied to the information generated by CPSC cannot be applied to external information sources

EPA at pages 14-17 of its proposed guidelines exempts from the Data Quality guidelines most third-party information submitted to the agency.

(6) Definition of "Affected Persons"/Definition of a "Person"

The definition of an "affected person" is fundamental to the operation of the Data Quality Act because it determines who is eligible to file an administrative petition for correction of agency-disseminated information.

OMB's interagency Data Quality guidelines concluded that "affected persons are people who may benefit or be harmed by the disseminated information. This includes persons who are seeking to address information about themselves as well as persons who use information." 66 FR 49718, 49721 (Sept 28, 2001). Individual agencies should use OMB's broad definition, which is consistent with the intent of these guidelines: to provide the public with a right to agency disseminated information that meets high Data Quality standards; and with a right to correct any publicly disseminated information that does not meet these standards.

Example(s) of Satisfactory Agency Proposals

OMB

OMB's definition of "affected persons" encompasses anyone who benefits or is harmed by the information including, "both:(a) persons seeking to address information about themselves or about other persons to which they are related are associated; and (b) persons who use the information." OMB's definition is further detailed by their comprehensive definition of "person" which includes individuals, organized groups, corporations, international organization, and governments and government agencies.

Example(s) of Unsatisfactory Agency Proposals

Department of Commerce

Commerce, at 67 FR 22398, 22401, (May 3, 2002), proposes to define "affected person" in an extremely narrow manner:

(1) *Affected person* means a person who meets each of the following three criteria:

(i) The person must have suffered an injury "harm to an identifiable legally-protected interest [sic];

(ii) There must be a causal connection between the injury and the disseminated information-the injury has to be fairly traceable to the disseminated information or decision based on such information, and not the result of independent or unrelated action; and

(iii) It must be likely, as opposed to merely speculative, that the injury will be redressed by a favorable decision.

Department of Labor

The Department of Labor provides no definition of "affected persons."

(7) Deadline for Deciding a Petition

Setting an appropriate, specific timeframe for agency decisions on information correction petitions is necessary to fulfil one of the key purposes of the Data Quality Act amendments of the PRA – enabling parties to obtain correction of information. It is also required by OMB's guidelines.

Example(s) of Satisfactory Agency Proposals

Multiple Agencies

Agencies including HHS, the Social Security Administration, and the Nuclear Regulatory Commission have proposed a 45-working-day time limit for the responsible agency to respond to the petition with either: (1) a decision; or (2) an explanation of why more time is needed, along with an estimated decision date.

The HHS and similar proposals are cognizant of: (1) agency responsibility to respond in a timely and informative manner to all petitioners; and (2) that some petitions may require a longer timeframe for a response. These proposals provide agencies with flexibility without allowing open-ended delays in deciding a petition. It should be noted that these proposed guidelines do not include provisions allowing additional response extensions.

Example(s) of Unsatisfactory Agency Proposals

Department of Labor

DOL's proposed guidelines state that the agency should "try to respond to complaints and appeals within ninety (90) days of their receipt, unless they deem a response within this time period to be impracticable, in light of the nature of the complaint and the agency priorities."

DOL's proposal does not require any communication to the petitioner and allows for open-ended delays in responding to requests for correction of information.

(8) Who Decides the Initial Petition?

The selection of the party responsible for acting on information correction petitions is important because this person will have a substantial responsibility for ensuring that one of the primary intents of the PRA is realized – allowing affected persons to obtain necessary correction of federally disseminated information.

Example(s) of Satisfactory Agency Proposals

The Federal Housing Finance Board

The FHFB's proposed guidelines state that the Board's "Chief Information Officer and other personnel responsible for the information will review the underlying data and analytical process used to develop the disputed information to determine whether the information complies with OMB and agency Guidelines and whether and how to correct the information, if appropriate." P. 6.

The FHFB's short correction process statement has several important strong points including: (1) designation of an official with primary responsibility for the correction who did not originate the information; (2) examination of the data in question and the process used to produce it; and (3) determination of whether the information complies with the Data Quality requirements of both the agency and OMB.

Example(s) of Unsatisfactory Agency Proposals

National Science Foundation

NSF does not provide any indication as to the official or organization within the agency responsible for acting on information correction petitions. Other agencies, including the Department of Labor and CFTC provide little or no information on who is responsible for evaluating information correction petitions.

Without knowing who has responsibility for the information correction process, it is difficult to evaluate that process. Furthermore, by failing to indicate the official/organization responsible evaluating information correction petitions, the agencies raise questions as to the extent to which they have thought through their process.

(9) Who Decides Appeals?

The appeal is the last administrative process open to an affected person seeking correction of information. Thus, to fulfill congressional and OMB intent with regard to ensuring the quality of disseminated information, it is important that agencies have a meaningful appeals process that is able to catch any errors which may have made it through both the initial dissemination quality review and the initial information correction process.

Example(s) of Satisfactory Agency Proposals

Securities and Exchange Commission

The SEC's proposed appeals process (referred to as a "request for staff reconsideration") routes the appeal to an official (usually in the Office of General Counsel) who was not involved in either producing the original data in question or in making the decision on the original request. The SEC's proposal also allow the appeal official to seek the advice of other officials.

The SEC's proposal ensures that the decision on any appeal is made by an objective official.

Example(s) of Unsatisfactory Agency Proposals

Department of Treasury

The Department of Treasury has proposed that any administrative appeal of an information correction petition be conducted "... within the Bureau (or Departmental Office), which disseminated the information." P.6.

By failing to provide for independent review of administrative appeals, Treasury's proposal: (1) reduces the likelihood of any errors being recognized on appeal because the appeal would be performed by the same organization which handled both the initial dissemination and the original complaint; and (2) creates a potential conflict of interest.

(10) Must the Agency Correct Information When It Agrees with a Petition?

The Data Quality Act amendments to the PRA explicitly gives the public the right to seek and obtain correction of federally disseminated information. Thus, to comply with the law, agencies should be required to correct information disseminations covered by the guidelines.

Example(s) of Satisfactory Agency Proposals

Department of Defense

DOD's proposed guidelines state, "If the PAA [Public Affairs Activity of the relevant DOD Component] agrees with any portion or all of a complainant's request, he will notify the disseminator of the information that the correction must be made, and shall explain the substance of the requested correction. The PAA shall inform the requester, in writing, of the decision and the action taken." Sec. 3.3.5.1.

DOD's proposed guidelines recognize that when a request for an information correction is valid, the information "must" be correct. The DOD procedures would also ensure that the petitioner is informed of the action.

Example(s) of Unsatisfactory Agency Proposals

Department of Labor

DOL's proposed guidelines indicate that, when there is a valid request for information correction, the Department's response will be based on a number of loosely-defined factors including "the agency's more pressing priorities and obligations." P.7.

DOL's proposed guidelines would not implement the Act's legal requirement that affected parties be able to obtain correction of erroneous information. Although under OMB's guidelines agencies "are required to undertake only the degree of correction that they conclude is appropriate for the nature and timeliness of the information involved....," the OMB guidelines do not create exemptions from the correction requirements due to "more pressing issues." 67 F.R. 8452, 8458.

(11) What is the Standard for Rebutting the Presumption of Objectivity Resulting from Peer Review?

The OMB guidelines state that information will generally be presumed to be objective if data and analytic results have been subjected to formal, independent peer review; however, this presumption is rebuttable "based on a persuasive showing by a petitioner in a particular instance." 67 F.R. 8452, 8454. The OMB guidelines also specify certain standards for agency-sponsored peer reviews. The issue is what will be considered a "persuasive showing" that will overcome the presumption of objectivity under the proposed agency guidelines. For example, if the agency does not comply with majority peer review criticism, views, or recommendations, does a presumption objectivity apply?

Example(s) of Satisfactory Agency Proposals

None

The closest satisfactory example, perhaps, is the DOL proposal, which simply adopts the exact language of the OMB guidelines: "rebuttabal based on a persuasive showing by the petitioner in a particular instance". App. II sec. 3, b, i.

Example(s) of Unsatisfactory Agency Proposals

Multiple Agencies

EPA's proposed does not address this issue.

The HHS proposal, the CDC/ATSDR proposal, and the NIH proposal do not address this issue.

The DOT proposal does not address this issue.

The CPSC proposal does not even mention peer review.

(12) How is "Influential Information" Defined?

The OMB guidelines define the term "influential;" however, they also provide agencies with some flexibility in adopting their own definition. The OMB guidelines state that "influential" "means that the agency can reasonably determine that dissemination of the information will have or does have a clear and substantial impact on important public policies or important private sector decisions." 67 F.R. 8452, 8455. The guidelines then state that "[e]ach agency is authorized to define "influential" in ways appropriate for it given the nature and multiplicity of issues for which the agency is responsible." *Id.* The issue is whether, and how, agencies have deviated from the OMB definition in proposing their own definition of "influential scientific, financial, or statistical information.

Example(s) of Satisfactory Agency Proposals

EPA

The closest to a satisfactory approach might be considered to be EPA's although it could be considered overly restrictive.

EPA adopts the OMB language, and then specifies several types of information that will generally be considered "influential," such as those that appear to meet the definition of a significant regulatory action, including an economically significant action, under E.O. 12866, and major scientific and technical work products undergoing peer review.

Example(s) of Unsatisfactory Agency Proposals

Multiple Agencies

The HHS proposal simply defines "influential" in the same way as OMB, adding, like OMB, that each of its subsidiary agencies is free to define "influential" in way appropriate for it given the nature and multiplicity of issues for which the agency is responsible. Secs 2), I and 4), d.

The CDC/ATSDR proposal does not contain an definition of "influential."

The NIH proposal defines "influential" in close conformity with the OMB interim final and final guidelines. Sec. VII.

The DOT proposal contains a very extensive discussion of the meaning of "influential," extending for almost two pages. In general, the discussion appears to be intended to restrict the situations in which the "influential" requirements will be applied. For example, broad impact is

required, so that substantial impact on individual companies would not be included, and the economic impact benchmark is the $100 million per year from the "economically significant" regulatory action portion of E.O. 12866. Other aspects of the definition of "significant regulatory action" from E.O. 12866 are also incorporated. Sec. XI, a.

DOL has an interesting qualification to "influential": "Whether information is influential is to be determined on an item-by-item basis rather than by aggregating multiple studies, documents, or other informational items that may influence a single policy or decision." DOL then defines "influential" using the OMB language, but also provides examples of what meets the definition and what does not. Among the examples of non-influential information products are "fact sheets", "technical information issuances", "accident prevention bulletins", and "studies". Sec. titled "Information Categories".

The CPSC guidelines do not define "influential." They simply refer to the OMB guidelines.

(13) What is "Objective" and "Unbiased" Information on Risks to Human Health, Safety and the Environment?

The Data Quality Act requires agencies to issue guidelines ensuring and maximizing the "objectivity" of all information they disseminate. The OMB guidelines implementing the legislation define "objectivity," and that definition includes a requirement that information be "unbiased" in presentation and substance. "Objectivity," along with "unbiased," is correctly considered to be, under the OMB guidelines, an "overall" standard of quality. 67 Fed. Reg. 8452, 8458. However, the OMB guidelines do not provide any explanation of how to eliminate bias from risk assessment.

For many years, risk assessments conducted by EPA and other federal environmental agencies have been criticized for being biased by the use of "conservative," policy-driven, "default assumptions", inferences, and "uncertainty factors" in order to general numerical estimates of risk when the scientific data do not support such quantitation as accurate. When such numerical assumptions are presented in any agency risk characterization, it is likely that members of the public who are unfamiliar with how the agency arrived at such numbers believe that the numbers are based on "sound science." In actuality, the risk numbers are a result of co-mingling science with policy bias in a manner such that they cannot be disentangled. The question is whether the proposed agency guidelines have attempted to address this issue and how.

Example(s) of Satisfactory Agency Proposals

None

None of the agencies have attempted to address this issue directly. The least objectionable proposal guidelines are those of agencies such as DOT and CPSC, which simply state that the information they disseminate must be "objective" and "unbiased," in accordance with the OMB guidelines.

Example(s) of Unsatisfactory Agency Proposals

A number of agencies appear to have attempted to effectively avoid this issue in order to continue the practice of employing default assumptions, inferences, and uncertainty factors to generate speculative risk numbers which they believe are necessary to ensure protection of public health. It appears they believe it is necessary to exaggerate risks in order to protect the public, rather than accomplishing that goal through the risk management decisionmaking process by making explicit policy decisions that are clearly separated from the presentation of scientific data and analysis.

Three agencies' proposed guidelines are examples: EPA, DOL/OSHA, and HHS/CDC/ATSDR. The three proposals bear a strong resemblance to each other. First, in discussing the requirements for risk assessments, they do not refer to the requirement for "objectivity" and "unbiased" data and presentation. Instead, they imply that OMB's requirement to adopt or adapt the quality standards from the Safe Drinking Water Act Amendments substitutes for that requirement. Accordingly, all three agencies state that presentations of risk information must be "comprehensive, informative, and understandable," rather than "objective" and "unbiased."

EPA goes a little further, referring to the use of "assumptions" and incorporating by reference its Science Policy Council Handbook on Risk Characterization. This Handbook was published in December 2000 but is based on its 1995 internal guidance.[1] This EPA risk characterization guidance makes clear that the agency will use policy-driven default assumptions, inferences, and uncertainty factors to generate risk characterizations (*e.g.*, pp. 15, 18, 21, 41, and C-24 of the Handbook and pp. 2 and 3 of the Administrator's Mar. 21, 1995 Memorandum), while at the same time stating that risk characterizations should be "separate from any risk management considerations" (Mar. 1995 Policy Memorandum, p.2) and that numerical risk estimates should be "objective and balanced" (*id.* at p. 4). One passage from the EPA risk characterization Handbook, incorporated into its proposed Data Quality guidelines, is particularly illuminating:

> **3.2.9 How Do I Address Bias and Perspective?**
>
> There is an understood, inherent, EPA bias that in the light of uncertainty and default choices the Agency will decide in the direction of more public health protection than [sic] in the direction of less protection. However, it is not always clear where such bias enters into EPA risk assessments. To the extent it may make a difference in the outcome of your assessment, highlight the relevant areas so that impact will not be overlooked or misinterpreted by the risk manager.

Handbook, p. 41. Nothing is said about such agency "bias" being overlooked or misinterpreted by the public. In addition, the statement confuses risk management ("protection") with risk "assessment," contrary to other statements of agency policy as indicated above. Inclusion of such readily acknowledged "bias" in agency risk assessments and characterizations disseminated to the public is directly contrary to both the Data Quality legislation and the OMB guidelines. The SDWA amendment quality standards do not take the place of the legislative requirements, interpreted and implemented by OMB, that risk assessments, along with all other agency information disseminated to the public, must be "objective" and "unbiased" as an "overall" quality standard.

---

[1] This risk characterization guidance was never subjected to public notice and comment, and the EPA proposed Data Quality guidelines do not inform the public regarding how to obtain it online. The document can be found at www.epa.gov/osp/spc/2riskchr.htm along with two related policy memoranda from 1995.

(14) Application of the SDWA Health Risk Assessment Standards

OMB's February 22nd agency-wide guidelines stated that the science quality and risk assessment standards contained in the 1996 amendments to the Safe Drinking Water Act (SDWA), 42 U.S.C. § 300g-1(b)(3)(B), should be adopted or adapted by federal agencies. Agencies should adopt both the SDWA science quality and risk assessment standards unless they conflict with the other federal statutory requirements. If such conflicts do arise, agencies should make every efforts to reconcile the SDWA standards with the conflicting statutory requirements.

There are only two valid reasons why a federal agency should not adopt these standards:

- The agency does not conduct health risk assessment; or
- The SDWA risk assessment standards conflict with the specific risk assessment standards of another federal statute governing the agency.

In the latter case, the agency should identify the conflicting specific risk assessment standards; make every effort to reconcile the conflicting standards with the SDWA standards; and request public comment on both the conflict and the attempt at reconciliation.

Example(s) of Satisfactory Agency Proposals

None

Example(s) of Unsatisfactory Agency Proposals

EPA

EPA's proposed guidelines state that EPA will only adapt the SDWA risk assessment standards, without explaining how or why.

(15) Robustness Checks for CBI

OMB's February 22nd interagency Data Quality guidelines require robustness checks for data, models, or other information that the agency cannot disclose, but which are material to information that the agency does disclose. These robustness checks are critical for ensuring compliance with the Data Quality Act because the public will not be afforded any other mechanism for determining the objectivity, utility, and reproducibility of this non-disclosed information, which underlies disclosed information. OMB explained in its February 22nd agency-wide guidelines that the "general standard" for these robustness checks is "that the information is capable of being substantially reproduced, subject to an acceptable degree of imprecision." 67 FR 8452, 8457. Moreover, agencies must disclose "the specific data sources that have been used and the specific quantitative methods and assumptions that have been employed." *Id.*

Moreover, agency robustness checks for confidential business information (CBI) or proprietary models should be subject to the Data Quality Act petition process.

Consequently, agency guidelines should state:

- Agencies will perform robustness checks meeting OMB's general standard set forth above.
- Agencies will provide sufficient information to the general public to determine whether that standard has been met.
- The agency's compliance with these requirements is enforceable through the Data Quality Act petition process.

Example(s) of Satisfactory Agency Proposals

None

Example(s) of Unsatisfactory Agency Proposals

Multiple Agencies

Most agencies' proposed guidelines are very vague on the robustness check issue, and none specifically state that the agency's robustness checks, or lack thereof, are subject to the Data Quality Act petition process.

(16) Use of Third-Party Proprietary Models

Federal agencies often use various models developed by third parties (often government contractors) to formulate policies based upon influential scientific information. The third-party models are sometimes asserted to be confidential and proprietary.

This issue does not involve the concerns that arise when regulated entities are required to submit confidential or proprietary data to an agency pursuant to a regulatory program. Instead, this issue is limited to situations where any agency and a contractor agree to use a model on a proprietary basis to develop influential scientific information.

OMB's interagency Data Quality guidelines require that influential scientific information be reproducible. This reproducibility standard generally requires that the models used to develop such information be publicly available. The OMB guidelines further explain that when public access to models is impossible for "privacy, trade secrets, intellectual property, and other confidentiality protections,: an agency "shall apply especially rigorous robustness checks to analytic results and documents what checks were undertaken." 67 F.R. 8452, 8457.

RECOMMENDED SOLUTION

General Policy

- Federal agencies should adopt a general prohibition against use of third-party proprietary models in their Data Quality Act guidelines.
- Use of third-party proprietary models conflicts with the goals and intent of the Data Quality Act.
- Public disclosure of third-party models should be required in all but the most unusual circumstances.
- If federal agencies believe they must use third-party proprietary models in order to carry out their regulatory duties and functions, then they should have the burden of demonstrating to OMB, before entering into a contract to use the model, that no other option is available.
- Federal agencies' Data Quality guidelines should explain in detail what "especially rigorous robustness checks" will be applied to third-party proprietary models that the agencies and OMB agree must be used and explain how the public will be informed of these "robustness check." The public should be allowed to review and comment on these robustness checks.

Implementation of the General Policy

Prospective Implementation:

Federal agencies should propose and promulgate Data Quality guidelines declaring the general policy on this issue as described above. These guidelines should further state that, before the agencies agree to use a third-party, non-public, proprietary model, they will provide OMB a written justification as to why the agencies have no other option, and await OMB's views before entering into a contract that utilizes an allegedly proprietary model. The written justification to OMB should describe why the agencies cannot:

- Use an existing public model;
- Enter into a contact to develop a new public model;
- Reimburse a contractor so as to convert a proprietary model into a public model.

Agencies should provide public notice of and an opportunity to comment on the above justification.

Retroactive Implementation:

If a federal agencies has already agreed to use a third-party proprietary model before it proposes Data Quality guidelines, then the agency should undertake the following actions within 45 days of the date it sends its proposed Data Quality guidelines to OMB for review.

- Provide OMB with a written identification of what third-party proprietary models are being sued by the agency;
- Provide OMB with a written explanation of why the agency cannot reimburse the contractors so as to convert third-party proprietary models into public models, or enter into a contract to develop a public model.

Agencies should provide public notice of and an opportunity to comment on the above justification.

LAW OFFICES

MULTINATIONAL LEGAL SERVICES, PLLC
11 DUPONT CIRCLE, N.W.
WASHINGTON, D.C. 20036
(202) 797-7124

FACSIMILE: (202) 939-6969

MEMORANDUM

To: The Center for Regulatory Effectiveness

From: Scott Slaughter, Esq.
Multinational Legal Services

Date: May 29, 2002

Subject: Federal Agency Authority to Create Exemptions from the Data Quality Guidelines that are Required by the Paperwork Reduction Act's Information Dissemination Provisions

---

I. QUESTION PRESENTED

Can the Office of Management and Budget ("OMB") or any other federal agency exempt any publicly disclosed information from data quality guidelines promulgated under the Information Dissemination provisions of the Paperwork Reduction Act ("PRA"), 44 U.S.C. §§ 3504(d)(1), 3516 note?

II. ANSWER

No. As explained below, the relevant statutory text and legislative history demonstrate clear congressional intent that these data quality guidelines, like the PRA's other Information Dissemination requirements, apply to any and all information that federal agencies have in fact made public. By contrast to the PRA's separate Collection of Information requirements, there are no statutory exemptions from any of the PRA's Information Dissemination requirements. OMB's attempt to create exemptions by restricting the definition of "dissemination" in its interagency data quality guidelines contradicts Congress' own pervasive and all encompassing use of this term. OMB's "dissemination" exemptions in its interagency data quality guidelines are also inconsistent with OMB's prior, much broader definition of "dissemination"in implementing the PRA's Information Dissemination requirements. The additional exemptions proposed by other federal agencies also violate clear Congressional intent because OMB cannot provide any exemptions from its interagency data quality guidelines, and the other agencies have to comply with OMB's interagency guidelines.

III. BACKGROUND

The PRA's Information Dissemination requirements are separate from the PRA's Collection of Information requirements. *E.g.*, 44 U.S.C. §§ 3502(3), (12); 3504(c),(d); 3506(c),(d). One express purpose of the PRA's Information Dissemination requirements is to:

> ... improve the quality and use of Federal information to strengthen decisionmaking, accountability, and openness in Government and society.

44 U.S.C. § 3501(4).

The legislative history accompanying the 1995 PRA amendments that added most of the Information Dissemination requirements, H.R. 830, 104th Cong. (1995), explains that these amendments "promote[] the theme of improving the quality and use of information to strengthen agency decisionmaking and accountability and to maximize the benefit and utility of information created, collected, maintained, used, shared, disseminated, and retained by or for the Federal Government."

H. Rep. No. 104-37, at 35 (Feb. 15, 1995) ("House Report").

The recently enacted Data Quality Act, 44 U.S.C. § 3516 note, does not affect the PRA's Collection of Information requirements. Instead, it amends the PRA's Information Dissemination requirements in several respects. *Id.*

First, the Data Quality Act establishes statutory deadlines for OMB's promulgation of interagency data quality guidelines under section 3504(d)(1), 44 U.S.C. § 3504(d)(1), of the PRA's Information Dissemination requirements, and under OMB's PRA rulemaking authority provided by section 3516. 44 U.S.C. § 3516 note.

Second, the Data Quality Act requires that OMB's interagency data quality guidelines "provide policy and procedural guidance to federal agencies for ensuring and maximizing the quality, objectivity, utility, and integrity of information (including statistical information) disseminated by Federal agencies...." *Id.*

Third, the Data Quality Act requires that OMB's interagency data quality guidelines "shall...apply to the sharing by Federal agencies of, and access to, information disseminated by Federal agencies...." *Id.*

Fourth, the Data Quality Act requires that all federal agencies subject to the PRA promulgate their own data quality guidelines by a statutory deadline. *Id.* These individual agency data quality guidelines must comply with OMB's interagency section 3504(d)(1) guidelines. 44 U.S.C. §§ 3504(d)(1); 3506 (a)(1)(B); 3516 note.

Fifth, the Data Quality Act requires that OMB's interagency data quality guidelines require all federal agencies subject to the PRA to establish administrative processes allowing "affected persons to seek and obtain correction of information maintained and disseminated by the agency that does not comply with" OMB's interagency guidelines. 44 U.S.C. § 3516 note.

OMB has now promulgated PRA section 3504(d)(1) interagency data quality guidelines. 67 FR 8452 (Feb. 22, 2002)(final OMB guidelines); 66 FR 49718 (September 28, 2001)(Interim Final OMB data quality guidelines explain that they are issued "'under sections 3504(d)(1) and 3516'" of the PRA). The other federal agencies subject to the PRA are now proposing their own PRA data quality guidelines. *E.g.*, 67 FR 21234 (April 30, 2002)(EPA's proposed data quality guidelines).

OMB's interagency data quality guidelines exempt from their coverage certain publicly disclosed federal agency information:

> "Dissemination" means agency initiated or sponsored distribution of information to the public (see 5 CFR 1320.3(d) (definition of "Conduct or Sponsor")). Dissemination does not include distribution limited to government employees or agency contractors or grantees; intra- or interagency use or sharing of government information; and responses to requests for agency records under the Freedom of Information Act, the Privacy Act, the Federal Advisory Committee Act or other similar law. This definition also does not include distribution limited to correspondence with individuals or persons, press releases, archival records, public filings, subpoenas or adjudicative processes.

67 FR 8452, 8460. The regulation referenced by OMB, "5 CFR 1320.3(d)," only applies to the PRA's Collection of Information requirements.

This definition of "dissemination" is considerably narrower than OMB's previous definitions of this term in a PRA Information Dissemination context. For example, in OMB Circular A-130, at page 3, OMB defined "dissemination" to mean:

> the government initiated distribution of information to the public. Not considered dissemination within the meaning of this Circular is distribution limited to government employees or agency contractors or grantees, intra-or inter-agency use or sharing of government information, and responses to requests for agency records under the Freedom of Information Act (5 U.S.C. 552) or Privacy Act.

Other agencies have included the OMB exemptions in their proposed data quality guidelines. Some agencies have proposed to expand the OMB exemptions, or to add new exemptions. For example:

Retroactivity Exemption. Several agencies, such as NIH at page 4, make statements indicating that their guidelines, and the OMB guidelines, will apply only to information that is disseminated initially after October 1, 2002. This proposed exemption contradicts OMB's interagency guidelines which specify that they apply to information created or originally disseminated prior to October 1, 2002 if an agency continues to disseminate the information after that date.

Case-By-Case Exemption. Several agencies, including EPA at pages 22-23 of its proposed guidelines, propose application of the PRA's data quality guidelines on a case-by-case basis, rather than application of them to all information disseminated by the agency.

Rulemaking Exemption A number of agencies, including EPA at pages 22-23 and the Treasury Department at page 6 of their proposed guidelines, have stated that the data quality error correction process required by OMB's interagency data quality guidelines will not apply to information in proposed rulemakings, and that any alleged errors will be addressed only through the rulemaking notice and comment process. It is not clear from these proposed exemptions whether the agencies believe that any of the PRA's data quality standards apply to information disseminated during rulemakings.

Adjudicative Processes Exemption. EPA's proposed data quality guidelines, at page 17, substantially expand the adjudicative processes exception by broadening it to include, *inter alia*:

> Distribution of information in documents relating to any formal or informal administrative action determining the rights and liabilities of specific parties, including documents that provide the findings, determinations or basis for such actions. Examples include the processing or adjudication or applications for a permit, license, registration, waiver, exemption, or claim; actions to determine the liability of parties under applicable statutes and regulations; and determination and implementation of remedies to address such liability.

IV. THE PRA'S DATA QUALITY GUIDELINES APPLY TO ALL INFORMATION THAT FEDERAL AGENCIES HAVE IN FACT MADE PUBLIC; NEITHER OMB NOR ANY OTHER AGENCY HAS DISCRETION TO CREATE ANY EXEMPTIONS

OMB's interagency data quality guidelines implement section 3504(d)(1) of the PRA. 44 U.S.C. § 3516 note. Section 3504(d)(1) requires that "with respect to information dissemination, the [OMB] director shall develop and oversee the implementation of policies, principles, standards, and guidelines to apply to Federal agency dissemination of public information, regardless of the form or format in which such information is disseminated...." 44 U.S.C. § 3504(d)(1). All federal agencies subject to the PRA must comply with OMB's interagency data quality guidelines. 44 U.S.C. §§ 3504(d)(1); 3506 (a)(1)(B); 3516 note.

The legislative history of the PRA's Information Dissemination requirements states congressional intent that "the legislation's policies and required practices apply to the dissemination of all Government information regardless of form or format...." House Report, at 27. This statement of congressional intent occurs in a section of the House Report subtitled "Information Dissemination." House Report, at 26.

The relevant statutory text and legislative history demonstrate clear congressional intent that there is only one restriction on the terms "disseminated" or "dissemination": they only apply to information that an agency in fact makes public.

The PRA defines "Public Information," as used in the PRA's Information Dissemination provisions, to mean "any information, regardless of form or format, that the agency discloses, disseminates, or makes available to the public." 44 U.S.C. § 3502(12)(emphasis added). The dictionary defines "any" to mean "every; all." *The Random House Dictionary of the English Language*, Second Edition, Unabridged (1983). The legislative history of the 1995 Act that added most of the PRA's Information Dissemination provisions explains that:

> The term "public information" is added. It means any information, regardless of form or format, that an agency discloses, disseminates, or makes available to the public. Its application in the act, as amended by this legislation, is primarily in the context of "dissemination" of information by an agency.

House Report, at 38.

The House Report contains a section entitled, "Additional Views on Information Dissemination Provision of H.R. 830." This section restates the legislative history of H.R. 3695, which passed the House at the end of the 101st Congress, but on which the senate took no action. H.R. 3695 contained most of the Information Dissemination provisions enacted by H.R. 830, "and much of the policy remains identical." House report, at 105. This section reiterates and reemphasizes the all-encompassing scope of the PRA's Information Dissemination requirements:

> H.R. 830 focuses on dissemination of information by agencies. "Dissemination" refers to the distribution of government information to the public through printed documents or through electronic and other media."
>
> ***
>
> H.R. 830 amends § 3502 of title 44 by adding paragraph (12) defining the term "public information" as "any information, regardless of format, that an agency discloses, disseminates, or makes available to the public."
>
> The concept of "public information" is fundamental to the information dissemination provisions of H.R. 830. The objective of the definition is to minimize disputes over what government information is subject to dissemination. The definition turns

on an easily made factual determination rather than a complex legal one. "Public information" is information that an agency has in fact made public.

House Report, at 107, 109.

The only restriction on the PRA's Information Dissemination requirements is that they only apply to information that agencies have in fact disseminated to the public:

> Dissemination obligations are limited to those classes of information already publicly disclosable because of a law, agency rule or regulation, or existing agency policy or practice. Thus, no dissemination obligation arises with respect to information classified in the interest of national defense or foreign policy, information subject to restrictions under the Privacy Act of 1974, sensitive law enforcement investigatory data, or other information withheld from disclosure to protect other recognized public or privacy interests.
>
> ***
>
> [A]n agency with an obligation to collect securities or tariff filings and to make those documents publicly available is clearly dealing with public information under the definition. Even if a portion of the filings is not public, the dissemination obligation attaches to the remainder if the class of public information can be identified and is routinely released.

House Report, at 109-10.

Congress' clear intent to include within the PRA's Information Dissemination requirements all information that an agency has made public is consistent with Congress' use of the term "dissemination" in other statutes. *See* Telecommunications Research and Action Center v. FCC, 836 F. 2d 1349, 1351(D.C. Cir. 1988)(under the Federal Communications Act, "dissemination" of radio communications becomes broadcasting subject to FCC licensing requirement when it is intended to be received by the public); U.S. Satellite Broadcasting Co., Inc. v. FCC, 740 F. 2d 1177, 1186 (D.C. Cir. 1984)(same).

Congressional intent that the PRA's data quality guidelines and other Information Dissemination requirements apply to all information that an agency has made public is further demonstrated by the fact that there are no statutory exemptions from the PRA's Information Dissemination requirements. 44 U.S.C. §§ 3502(12); 3504(d)(1); 3516 note. By contrast, there are several statutory exemptions from the PRA's separate Collection of Information requirements. 44 U.S.C. §§ 3502(3)(B); 3518(c)(1). If Congress had intended to create any exemptions from the PRA's data quality standards and other Information Dissemination requirements, it would have done so expressly as it did for the PRA's separate Collection of Information requirements. *See* Russello v. United States, 464 U.S. 16, 23 (1983)(if Congress intended to restrict applicability of a particular statutory requirement, it would have done so expressly as it did with another requirement of the statute).

In sum, there is no basis for concluding that Congress intended any exemptions from the terms "dissemination" and "disseminated" when it used those terms in statutory "Information Dissemination" requirements from which there clearly are no exemptions. Given the statutory text and legislative history, neither OMB nor any other federal agency has discretion to create any exemptions from the data quality guidelines required by the PRA *See* U.S. Department of Defense v. Federal Labor Rel. Auth., 510 U.S. 487, 494 (1994)(FOIA represents a general congressional intent of full disclosure of government information and any exemption must be stated in clearly delineated statutory language); Dole v. United Steelworkers of America, 429 U.S. 26 (1990)(OMB has no discretion to interpret the PRA in a manner that conflicts with clear congressional intent).

Center for Regulatory Effectiveness

Suite 700
11 Dupont Circle, N.W.
Washington, D.C. 20036
Tel: (202) 265-2383 Fax: (202) 939-6969
www.TheCRE.com

May 10, 2002

Hon. Stephen L. Johnson
Assistant Administrator for Prevention,
Pesticides and Toxic Substances
U.S. Environmental Protection Agency
Mail Code 7101M
1200 Pennsylvania Ave.. N.W.
Washington, D.C. 20460

Re: The Data Quality legislation and OMB's final implementing guidelines have superceded and prohibited EPA's categorical ban on its consideration and use of "third-party" human volunteer clinical studies

Dear Mr. Johnson:

On December 14, 2001, EPA issued a press release announcing that it would not consider or rely on any "third-party" clinical human test data studies in its regulatory decision making pending the outcome of an EPA-requested National Academy of Sciences' review of unspecified issues involved in such studies. (A copy of the press release is attached as Exhibit A). The announcement also stated that the ban will continue following receipt of the NAS report while EPA formulates a formal policy on future acceptance, consideration or regulatory reliance on such human studies.

The NAS study has still not begun, and a subsequent agency rulemaking is likely to be lengthy and its outcome uncertain. It could well be several years, if ever, before the agency formulates a "formal policy". The December 14, 2001, EPA announcement imposing a ban on the use of such studies therefore amounts to an interim final rule under the APA definition. It is as final as can be for the foreseeable future, and may or may not be revised.

However, this December 14, 2001, interim final rule contains an important qualification. It states that the ban will not apply if EPA is "legally required" to consider or rely on any such human study during this interim period.

When the December 14 rule was issued, the Office of Management and Budget had not yet issued its final "guidelines" implementing the new Data Quality legislation. The final OMB

guidelines were issued on January 3, 2002, and reissued with corrections on February 22, 2002.[1] The legislation[2] and OMB rules are legally binding on all federal agencies, including EPA. Although denominated "guidelines", they clearly constitute legal requirements issued to implement Congressional mandates. Agencies are now in the process of developing agency-specific guidelines; but those guidelines must, as a matter of law, be in conformance with the legislation and the OMB rules.

There is no indication that EPA has yet considered the impact of the Data Quality legislation and OMB rules on its December 14, 2001 interim final rule banning use or reliance on human clinical studies.

As explained below, EPA is now "legally required" by the legislation and OMB rules to consider and appropriately incorporate "third-party" clinical human volunteer studies in risk assessments and related regulatory decisions.

Consequently, the Center for Regulatory Effectiveness now requests EPA to review its interim final ban on use of human volunteer clinical studies in light of the new OMB legal requirements.[3] We believe that those requirements clearly require that the agency now take the following actions to modify its December 14 policy statement:

- Announce that, in view of the new OMB rules, EPA has now determined it is legally required to consider and rely on such studies in its risk assessments and regulatory decisions if the studies are determined to have been conducted in accordance with generally accepted ethical standards and are scientifically relevant.[4]

- Announce that any such studies that have previously been reviewed and relied on by the Agency will be considered acceptable now for consideration and use by EPA in regulatory decision making.

- Refrain from taking any affected regulatory actions until EPA's current ban on consideration of third-party clinical human test data is modified or rescinded, and the new policy identified in this letter is implemented.

---

[1] 67 Fed.Reg. 369-78; 67 Fed.Reg. 8452-60.

[2] 44 U.C.C. § 3501 *et seq.* and § 515, P.L. 106-554; 44 U.S.C. § 3516 note.

[3] This request should be considered a petition for modification or recission of a rule under the APA, 5 U.S.C. § 553(e).

[4] Consensus ethical standards are already embodied in the Declaration of Helsinki and the federal Common Rule, which EPA subscribes to. The Common Rule even provides for acceptance of human studies conducted in accordance with the Declaration of Helsinki. It is not clear what EPA had in mind in requesting the NAS to consider ethical issues.

THE DATA QUALITY LEGISLATION AND OMB'S GUIDELINES REQUIRE EPA TO CONSIDER AND USE THE BEST AVAILABLE DATA AND STUDIES

The Data Quality legislation and OMB's implementing guidelines require that EPA disseminate information, including risk assessments, based on the best available data and studies, particularly if such data or studies have been peer-reviewed. This requirement stems in part from the "objectivity" standard imposed by the Act and OMB's guidelines. In order to meet this standard, risk assessments and other information disseminated by EPA have to be "accurate, clear, complete, and unbiased." 67 FR 8453, 8459. Disseminated information that excludes the available and relevant data and studies cannot be accurate, clear, complete and unbiased.

The OMB guidelines specifically address quality aspects of human health risk assessments. The guidelines require agencies to apply the quality standards specified by Congress in the Safe Drinking Water Act Amendments of 1996 ("SDWAA"). Agencies must either "adopt or adapt" these Congressional requirements in their agency-specific data quality guidelines. 67 Fed.Reg. 8457-58, 8460. The OMB guidelines make clear that use of the term "adapt" does not relieve agencies of the responsibility for applying these basic quality standards; rather, the term "adapt""is intended to provide agencies with flexibility in applying these principles to various types of risk assessment." 67 Fed.Reg. 8458 1st col.

The SDWAA quality principles specifically quoted in the OMB guidelines as applicable, and which are particularly relevant to the consideration and use of data from human volunteer clinical studies, include the following:

- "'[T]o the degree that an agency action is based on science'", the agency is directed "'to use...the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices...'" 67 Fed.Reg. 8457 3d col.

- The presentation of information in the risk assessment must be "'comprehensive'". *Id.*

- The risk assessment must specify, to the extent practicable, "'each significant uncertainty identified in the process of the assessment of [risk] effects and the studies that would assist in resolving the uncertainty'." 67 Fed.Reg. 8458 1st col.

- The risk assessment must also specify "'peer-reviewed studies known to the [agency] that support, are directly relevant to, or fail to support any estimate of [risk] effects . . . .'" *Id.*

Data and studies that have previously been peer-reviewed, including peer-review by the SAB or SAP, and relied upon in developing risk assessments and determining reference doses have already been "peer-reviewed' and require no further peer-review in order to comply with these principles.

HUMAN VOLUNTEER CLINICAL STUDIES PROVIDE SOME OF THE BEST AVAILABLE AND MOST RELIABLE DATA FOR EVALUATING HUMAN HEALTH RISKS

Attached as Exhibits B and C are two published articles by distinguished scientists which explain that clinical human test data are often the best available data on a substance or product's risk to human beings. This point is further demonstrated by the fact that EPA itself frequently conducts clinical human tests to assess risk, and has also frequently used third-party clinical human tests to assess risk. Ongoing EPA clinical human tests include those conducted at EPA's "inhalation chambers" in North Carolina where human volunteers, including asthmatics, are exposed to various air pollutants. (Exhibits D, E and F). The United States Court of Appeals for the District of Columbia recently relied on this type of EPA clinical human test to uphold the Agency's ozone standards under the Clean Air Act. *American Trucking Association, Inc. v. EPA*, 2002 WL 452092, *22 (D.C. Cir., March 26, 2002).

There is no rational basis for distinguishing categorically between clinical human tests conducted by EPA and by third parties. Therefore, under the Data Quality legislation and OMB's guidelines, EPA cannot disseminate risk information that categorically excludes consideration and use of third-party human volunteer clinical data and studies. For the same reasons, under the Data Quality legislation and OMB's guidelines, EPA cannot propose and promulgate guidelines that allow the categorical exclusion of third-party clinical human test data and studies.

CONCLUSIONS AND RECOMMENDATIONS

The agency's December 14, 2001, interim final rule banning consideration and use of human volunteer clinical studies has been superceded by the legal requirements contained in the final OMB guidelines on data quality. There is no conceivable way in which such studies can be excluded from the applicable OMB directives noted above. Accordingly, EPA should --

- Issue, as soon as possible, an announcement or notice acknowledging these new legal requirements and modifying or rescinding the ban contained in the December 14 announcement.

- Announce that any such studies that have previously been reviewed and relied on by the Agency will be considered acceptable now for consideration and use by EPA in regulatory decision making.

- Refrain from taking any affected regulatory actions until EPA's current ban on consideration of third-party clinical human test data is rescinded, and the new policy identified in this letter is implemented.

Thank you for your prompt consideration of this matter. Please feel free to contact me if you feel you need clarification of any of the points in this petition or wish to discuss it.

Sincerely,

Jim J. Tozzi
Member, CRE Board of Advisors

Attachments

cc (w. attach.):

Hon.Christine Todd Whitman
Hon. Kimberly T. Nelson, OEI/CIO
Marcia Mulkey, OPP
Philip J. Ross, OGC
Michele Knorr, OGC

EPA United States Environmental Protection Agency

Headquarters Press Release
Washington, DC

Date Published: 12/14/2001

Title: AGENCY REQUESTS NATIONAL ACADEMY OF SCIENCES INPUT ON CONSIDERATION OF CERTAIN HUMAN TOXICITY STUDIES; ANNOUNCES INTERIM POLICY

EPA

Environmental News

FOR RELEASE: FRIDAY, DECEMBER 14, 2001

AGENCY REQUESTS NATIONAL ACADEMY OF SCIENCES INPUT ON CONSIDERATION OF CERTAIN HUMAN TOXICITY STUDIES; ANNOUNCES INTERIM POLICY

Contact: David Deegan, 202-564-7839 / deegan.dave@epa.gov

In a letter released today, the Environmental Protection Agency is requesting that the

National Academy of Sciences conduct an expeditious review of the complex scientific and ethical issues posed by EPA's possible use of third-party studies which intentionally dose human subjects with toxicants to identify or quantify their effects.

EPA will ask the Academy to furnish recommendations regarding the particular factors and criteria EPA should consider to determine the potential acceptability of such third-party studies. Recently, most submissions to the Agency have concerned toxicity testing of pesticides, such as studies used to establish a No Observed Adverse Effect Level or No Observed Effect Level for systemic toxicity of pesticides. The Academy is also being asked to provide recommendations on whether internationally accepted protocols or the Protection of Human Subjects Rule ("the Common Rule," which details the protection of human subjects of EPA-conducted or supported research) could be applied to develop the scientific and ethical criteria for EPA to evaluate such studies. These third-party studies that will be the focus of the Academy review are those that have not been conducted or funded by a federal agency in compliance with EPA's Common Rule, or its equivalent.

"Our paramount concern in developing our policy on these studies must be protection of human health and adherence to the most rigorous ethical and scientific standards," said EPA Administrator Christie Whitman. "Formulating a policy that appropriately reflects our competing concerns in this matter will not be easy, and I thank the National Academy of Sciences for agreeing to assist EPA in evaluating these complex issues. The one thing that all parties agree upon is the need for EPA to formulate a formal policy on the use of human testing data, and we will do so in a transparent and responsible manner."

The Agency will ask that the Academy incorporate early in its review an open, public and participatory process through which all interested parties may raise their concerns and ideas for consideration. Following the Academy's review, EPA will engage in an open and participatory process involving federal partners, interested parties and the public during its policy development and/or rule making regarding future acceptance, consideration or regulatory reliance on such human studies.

During the Academy's consideration of the issues and until a policy is in place, the Agency will not consider or rely on any such human studies in its regulatory decision making, whether previously or newly submitted. Should EPA be legally required to consider or rely on any such human study during this interim period, the Agency will assemble a Science Advisory Board subpanel to review and comment on scientific appropriateness and ethical acceptability of the study in question, and the Agency will provide an opportunity for public involvement. This external review would occur prior to consideration of the study and would allow the Science Advisory Board to review all available information on the study.

Notwithstanding the interim policy, existing provisions of the Federal Insecticide, Fungicide, and Rodenticide Act and the Toxic Substances Control Act, continue to require industry to report any adverse effects information from such studies. In any instance where third-party human testing data suggests a public health concern, the

Agency would promptly consider that information.

Attachment

R-246 # # #

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460

December 14, 2001

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Dr. Bruce Alberts
President
National Academy of Sciences
2101 Constitution Avenue, NW
Washington. D.C. 20418

Dear Dr. Alberts:

I am writing to request that the National Academy of Sciences (NAS) provide recommendations to the Agency to help address the scientific and ethical questions related to whether to accept, consider, or rely on research involving deliberate exposure of human subjects to toxicants when used to identify or quantify toxic endpoints. The Agency asks that the Academy review these issues and provide recommendations that will help EPA develop appropriate factors and criteria to apply when it makes these difficult decisions. The advice of the Academy will be weighed heavily as we develop and implement a policy to govern these decisions in future.

The Agency's particular focus of concern is on studies which, since they are not conducted or supported by a federal agency, may not be performed subject to regulations that protect human subjects, such as EPA's Protection of Human Subjects Rule ("the Common Rule"), 40 CFR 26. We are particularly concerned about 'third-party' studies

submitted by regulated entities for the Agency's consideration. For these purposes, EPA is considering "third-party studies" as studies that have not been conducted or funded by a federal agency pursuant to regulations that protect human subjects. These types of studies generally come to the Agency's attention only after the research has been completed and reported. At this point it is generally too late for the Common Rule requirements to apply since these requirements cover prior review and approval of proposed research, involving fully informed, voluntary consent of the participants to protect the subjects in the research.

One particular concern of the Agency is for determining the acceptability of third-party research designed to identify or quantify toxic endpoints in human subjects, such as those done to define a No Observed Adverse Effect Level (NOAEL) or No Observed Effect Level (NOEL) for systemic toxicity in humans. Studies of this kind are submitted to the agency from time to time, and have been evaluated prior to regulatory decision in several Agency programs. In the recent past most such submissions have been of studies designed to define a NOAEL for pesticide toxicity in humans.

EPA asks the Academy to undertake a critical review of appropriate standards for the scientific and ethical assessment of research entailing deliberate dosing of human subjects with toxic agents. This review should incorporate and be informed by an early open, public, participatory process through which interested people can express their suggestions or concerns to the Academy reviewers.

The Agency subscribes fully to the principles of the Common Rule and the related rules of other federal agencies, as they protect the human subjects of research conducted or supported by the federal government. We are pleased with our record of compliance with the Common Rule in our own research, and of the favorable review by our human subjects protection program in a recent survey by the National Bioethics Advisory Commission.

The Agency will consider the Academy's advice resulting from this review as we develop a policy to guide its future decisions to accept, consider, or rely on such studies in regulatory decision making. As the Academy evaluates the scientific rationale and the ethical framework for these studies, it would be most helpful if the Academy would include in its general advice responses to the following questions:

- What factors should the Agency consider in determining whether to accept, consider, or rely on human studies performed by third parties? Are there clear boundaries between acceptable and unacceptable human research? If so, what are they? If not, what range of factors should the agency consider, and how should these factors be applied in making decisions to accept, consider, or rely on specific research?

- What range of information should the Agency consider in determining whether completed research with human subjects conducted by third parties was conducted

ce with the appropriate ethical standards, such as the Declaration of
hich may be cited in the research report?

such as those in the Common Rule provide an adequate framework for
e scientific and ethical acceptability of such studies? Should such a
signed to protect human participants in research, be applied after the
pleted research conducted by third parties to determine whether it is
as the basis for regulatory action?

ther standards, such as the Declaration of Helsinki or various standards
nical practice, relevant to assessing acceptability of research to define or
xic endpoints in human research subjects? Should standards intended to
nan safety studies for diagnostic or therapeutic agents be applied to
volving deliberate exposures to environmental toxins?

) meeting with you soon to work out the details and timing of your
constructive collaboration on this project.

son
nistrator

Colglazier
za

Email A
Comment

Human and Ecological Risk Assessment: Vol. 7, No. 6, pp. 1575-1581 (2001)

The Value of Human Testing of Pesticides

Ernest E. McConnell
ToxPath, Inc., 3028 Ethan Lane, Raleigh, NC 27615; Tel(voice): 919-848-1576, Tel(fax):919-848-1576

ABSTRACT

Recently, the issue of using human volunteers as subjects for studying the potential toxicity of pesticides has received public attention through the media and subsequently in the regulatory arena. The debate has focused on whether such studies are ethical *per se* and if data from these investigations should be used for regulatory decisions. The precipitating event that prompted the current debate was the enactment of the Food Quality Protection Act (FQPA) of 1996. The FQPA, which amended the two laws governing the regulation of pesticides in the United States, requires the Environmental Protection Agency to reassess all of the nearly 10,000 tolerances (maximum allowable residues in food) and exemptions from tolerances that were in place when the law went into effect. When reassessing tolerances the U.S. Environmental Protection Agency (USEPA) reviews the data, including toxicology, available on each pesticide to determine if they are adequate to allow the Agency to make the necessary safety finding. Historically, it had been considered acceptable to conduct and use data from studies of exposure to chemicals (including pesticides) of human volunteers if these studies were conducted according to specific criteria as outlined in the Helsinki Declaration and Common Rule. Now this philosophy is being challenged and the USEPA is faced with answering the question of whether pesticides should be viewed as different, from an ethical standpoint, from other chemicals, and how such data should be used in the risk assessment process.

The following paper makes an argument for the use of human volunteer testing of pesticides applying the logic that, if one wants to protect humans from the potential harm that may occur from eating foods containing pesticides, one must use the best possible data available. There can be little doubt that the best data for predicting the toxicity of a chemical in humans is to obtain and use human data, as long as it is obtained in an ethical manner.

Key Words: testing, human, pesticides.

INTRODUCTION

In my opinion, it seems only sensible to use human data, whenever possible, when determining the potential toxicity of any chemical to which the public is exposed.

1080-7039/01/$.50

This is particularly so for pesticide residues on foods because we are all potentially exposed to such foods. After all, pesticides, like many nonpesticide chemicals, are inherently toxic! One could make the argument, as some have, that the logical solution to this potential problem is to just ban the use of pesticides in food production. However, I submit that this is neither practical nor desirable. First, eliminating the use of pesticides in food production would dramatically increase the cost of most, if not all, types of food. While this increased cost would not be an undue hardship on affluent members of our society, it certainly would be for the less fortunate. Many pesticide-free foods (labeled as "organic") are increasingly available, and one should have the right to buy and consume such foods if he/she desires.

In addition to the economic considerations, in my view many types of food would not be as safe as they are with the use of pesticides. For example, before the development of pesticides that prevent damage to corn and peanuts with resulting mycotic infestation, mycotoxin contamination of these crops was a serious problem. Many of these mycotoxins are highly toxic and remain the cause of liver toxicity and liver and esophageal cancer in many parts of the world. Another example of how the use of pesticides has improved the quality and healthfulness of food is through the use of rodenticides and fumigants. Prior to their use, the loss due to bacterial contamination of food from rodents and insects during storage and handling was much greater than today. It would be impossible to store and ship foods as efficiently and safely as we do today without them.

I share the view of others that the abundance and relative low cost of foods that we enjoy today is a direct reflection of a combination of the use of pesticides, fertilizers, more efficient agricultural methods and the development of new and more productive strains and species of plants and animals. To delete pesticides from this equation would be counterproductive. That being the case, *i.e.*, that pesticides are an integral part of our food production and will continue to be for the foreseeable future, it is incumbent that we make sure that any residues that are present on food do not present a health hazard to humans consuming those foods. As noted before, pesticides are toxic chemicals, not unlike other chemicals to which we are exposed in our air, water and working environment.

In this context, I offer the following arguments in support of the value and need for the testing of pesticides in human volunteers. The logic underlying this view can be summarized in the simple paradigm below.

Protecting Humans = Human Risk Assessment = Best Possible Data = Human Data

PROTECTING HUMANS FROM THE POTENTIAL HAZARDS OF PESTICIDES

There is a long history in the United States of legislative and regulatory efforts to protect humans against the deleterious health effects from exposure to pesticides, as well as other chemicals. Before the Food Quality Protection Act was enacted (FQPA 1996), which probably represents the most significant and far-reaching piece of environmental legislation of the decade[1,2], pesticide residues in some processed foods were considered to be "food additives" and regulated under Section 409 of the

Federal Food, Drug and Cosmetic Act (FFDCA). If the pesticide residue was expected to exceed the tolerance level for a "raw" agricultural commodity allowed under FFDCA 408, it became necessary to establish a separate food "additive" regulation for the "processed" food under FFDCA 409. However the *Delaney Clause* in FFDCA 409 prohibited the establishment of food additive regulations for any substance "..."*if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal*". One of the primary reasons for enacting the FQPA was to address what was termed the *Delaney Paradox*, *i.e.*, regulating the presence of pesticides in *raw* and *processed* food differently.

FQPA solved this problem by unifying the setting of tolerances. Pesticide residues in both raw and processed foods are now regulated only under Section 408 of FFDCA, which does not contain a prohibition against setting tolerances for carcinogens. The Delaney Clause is no longer applicable for pesticides. Instead, FQPA provides for a single uniform health-based standard for pesticide residues in both types of foods; that is, that there should be "*reasonable certainty of no harm*" associated with exposure to residues in the food for which the tolerance is established.

Other noteworthy features of the FQPA are that this new safety standard, unlike the Delaney Clause, applies to *all health risks*, not just cancer. It also directs the USEPA to consider *cumulative effects* and *common mechanism of action* in its risk assessment. In practice "cumulative effects" involves the combining of exposures from the different routes of exposure, *e.g.*, inhalation, oral and dermal. Although a given source of pesticide exposure may involve primarily a single route of exposure, other routes may add to the overall dose. For example, if a person uses a can of insecticide spray in his/her house, there is a potential for inhaling the pesticide, getting it on one's skin or even on food in the vicinity. The total of these routes represents the true exposure to the individual. "Common mechanism of action" requires the Agency to combine, for risk assessment purposes, different kinds of pesticides if they work through a common mode of action. For example, if a person were exposed to several different types of organophosphate pesticides (OPs) that act via a common mode of action, *e.g.*, cholinesterase inhibition, then the different OPs would be totaled for exposure purposes in the risk assessment.

RISK ASSESSMENT

The object of this section is not to define or restate the risk assessment process, but to draw on those issues that impact the use and need for human data. There are essentially two separate evaluations that occur before one can be confident that a pesticide residue on food does not present a health hazard to the people consuming that food. The first step is to establish a *reference dose*, usually expressed in mg/kg body weight/day, which is a hazard value derived from the available toxicology database. This "reference dose" represents the maximum amount of daily exposure to all sources of that pesticide that can occur with "reasonable certainty of no harm". The second step is to establish a *tolerance level* for the pesticide. The "tolerance level" represents the amount of pesticide that is expected to remain on a given food at the time of harvest. Different tolerances may

be established for the same pesticide for different crops. If exposure at the tolerance level for a specific use were estimated to be greater than the reference dose, then it is likely that this particular application of the pesticide would not be allowed. If anticipated exposure from a new use would yield an *aggregate exposure* that exceeded the reference dose for the pesticide, this new use would not be approved unless adjustments, *i.e.*, exposure reduction or cancellation, were made in the already existing uses.

To establish the reference dose, the USEPA depends primarily on a series of required toxicity studies conducted in laboratory animals to characterize the potential human health risks that may ensue from exposure to pesticides. From these studies, the Agency selects the most appropriate endpoints of toxicity to use in risk assessment. If a "most appropriate" endpoint or species cannot be determined from the data set, then the Agency defaults to the use of the most sensitive endpoint(s) measured in the most sensitive sex/species to identify the highest dose that produces no adverse effects for this endpoint; referred to as the "No Observed Adverse Effect Level" (NOAEL). The Agency then uses this value as the basis for a series of mathematical exercises to estimate a "safe level" or, in the case of the FQPA, a level that would provide "reasonable certainty of no harm" in a similar fashion as is done by the Food and Drug Administration for setting safe levels for nonpesticide food additives.

As part of this mathematical exercise for setting the reference dose, the Agency uses additional "safety" or "uncertainty factors". First, if the best NOAEL is derived from an animal study, this NOAEL is divided by an uncertainty factor (10× is the default) to extrapolate from the animal to the human. This is referred to as the "*10× interspecies uncertainty factor*" and assumes that the human is more sensitive to exposure to the chemical than is the test animal. Then this number is divided further by another uncertainty factor (10× is again the default) to account for the range of sensitivities within the human population. This is called the "*10× intraspecies uncertainty factor*". In other words, the NOAEL by default is divided by at least 100 to set a reference dose for a given pesticide. Other uncertainty factors might also be required, if the data warrant. Traditionally, these additional factors were not needed when deriving a chronic reference dose (also known as the "acceptable daily intake" or an "acute reference dose") for a food use pesticide. This is what was required until passage and implementation of the FQPA.

However, another major part of the FQPA that is unique, and directly impacts on the issue of human testing, requires the USEPA to apply an additional "safety factor" of 10× when setting a pesticide reference dose for food to provide for special protection to children. In practice, this means that the NOAEL could be divided by 1000 or more for setting tolerances. The only way the additional 10× safety factor can be set aside (*not used*) is to have reliable scientific data that show that the developing fetus, infant and child are not uniquely different from adults in terms of the dose that produces a given effect. While this safety factor seems reasonable and supported by science (the young are often more at risk to harm than adults at a given dose), it can have profound ramifications on a given pesticide when setting the reference dose.

BEST POSSIBLE DATA

If the goal of the risk assessment process is to assure "reasonable certainty of no harm" from a pesticide residue in foods, then by default the most reliable data should be those that provide the most certainty that the risk assessment is an actual representation of potential risk. Although data from a myriad of animal and *in vitro* studies are submitted to the USEPA by the registrant, it needs to be remembered that these are not human data, although they certainly have application to humans. While animals have many of the same characteristics as humans in that they are reasonable surrogates for many of the toxicity endpoints of importance, they are not humans! Because of this, there is always, by necessity, a certain amount of uncertainty as to just how applicable the animal data are to humans. The best possible data to predict what would happen in humans as a result of exposure to pesticides from the handling and ingestion of foods are human data.

HUMAN DATA

There are two essential questions that need answering before discussing human data *per se*. First, what type of human studies provides the most relevant data for risk assessment, and second, can such data be obtained in an ethical manner? In practice, these two questions cannot be isolated from each other, but need to be considered in concert. For example, while there may be a given toxicology endpoint of interest, it may be impossible to obtain such data without causing harm to the human test subject. Obviously, one would not be interested in obtaining this type of data. In contrast, if one can obtain human data in a way that will not cause harm to the human subject, and if such data could benefit a risk assessment, then such data could be obtained and used.

While it is not the object of this paper to outline the procedures that are required for human studies, suffice it to say that human volunteer studies with pesticides, as with other chemicals, can be conducted in an ethical manner. There are several thoughtful arguments for why human testing is ethical, and highly specific criteria for how such studies should be conducted have been delineated (Declaration of Helsinki 1964, 1975, 1983 and 1989; Common Rule 1991). It needs to be remembered that there is nothing inherently unique about a pesticide in terms of its biological interaction that would suggest that human studies with such chemicals are any different than those conducted with nonpesticide chemicals. Once a pesticide enters the body, it behaves as would any other xenobiotic that interacted with the same organ, tissue or cell. As with other chemicals, pesticide toxicity is a direct reflection of its dose and biological target. Typically, the exposure chosen for human studies is a fraction of the most sensitive NOAEL or endpoint of interest derived from the animal studies. The human volunteer usually does not exhibit any clinical manifestation of exposure other than the presence of the material in his/her blood and urine.

In my opinion, as noted in the recent joint report of the USEPA FIFRA Science Advisory Panel and USEPA Science Advisory Board (USEPA 2000), the most appropriate type of data at this point would be in the area of absorption, distribution, metabolism and excretion (ADME). ADME data are easily obtainable in human

subjects without undue risk to the human volunteer participating in these studies. The value of these studies is that one can compare the findings with the same endpoints in the animal studies, thereby providing more or less confidence that the animal data are predictive of what might occur in humans. Additionally, such human data could provide insight for conducting additional animal studies that would give further assurance that the "total" data package provides the best chance to assure the public that their food supply has a "reasonable certainty of no harm" as required by the FQPA.

It may surprise the reader of this opinion that human studies are already required in some situations by the USEPA. The focus of these studies is to establish the level of exposure of workers engaged in mixing, loading, application and workers entering the field after pesticide application. It is noteworthy that these workers would be considered "volunteers" in that they have to give informed consent, *etc.* before the exposure analysis. However, the exposure conditions are not "controlled", in the same way as they would be in a toxicity study, *i.e.*, no pre-specified dose is "applied" to the worker. Exposure is only controlled and minimized by the use of specific types of clothing and other personal protective equipment. In addition, these studies typically do not include any toxicological evaluations, although measurements of biomarkers of exposure are increasingly being incorporated into the study design. However, logic would suggest that a well-controlled, scientifically based human volunteer toxicity study would be more appropriate to conduct *prior* to exposing workers. This view is particularly convincing when considering "new" pesticides that have not yet been introduced into commerce. The same could be said for pesticides that are used in and around the home. Why would one want to wait until the pesticide is already being used and people are being exposed before understanding the potential hazard to humans?!!

In summary, if, as noted previously, the seminal reason for conducting a risk assessment for pesticides in or on foods is to *protect humans* consuming these foods, then it only makes sense to obtain and use human data. If fact, one could make the argument that it is "unethical" not to use human data, as long as it is acquired in an ethical manner.

REFERENCES

Declaration of Helsinki. 1964, 1975, 1983, 1989. World Medical Association Declaration of Helsinki, III.4, as adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964. Amended by the 29th World Medical Assembly, Tokyo, Japan, Oct. 1975, the 35th World Medical Assembly, Venice, Italy, Oct. 1983, and the 41st World Medical Assembly, Hong Kong, Sept. 1989

Common Rule. 1991. Federal Register: Part 26-Protection of Human Subjects. 56 FR 28012, 28022. pp 26.101-26.124.s

FQPA (Food Quality Protection Act). 1996. Food Quality Protection Act. Pub.L., No. 104-170. 110 Stat. 1489.

Robertson HG and Gorovitz S. 2000. Pesticide toxicity, human subjects, and the Environmental Protection Agency's dilemma. J Contemp Hlth Law Policy. 16:427-58

USEPA (U.S. Environmental Protection Agency). 2000. Consideration of issues relating to the EPA's use of data derived from testing of human subjects. USEPA-SAB-EC-00-017. Washington, DC, USA

FOOTNOTES

1 The reader is directed to the USEPA OPP Website (http://www.epa.gov/pesticides) for more information on the FQPA.

2. The reader is directed to Robertson and Gorovitz (2000) for a detailed summary of the legislative and political history of the FQPA.

Regulatory Toxicology and Pharmacology 33, 234–256 (2001)
doi:10.1006/rtph.2001.1469, available online at http://www.idealibrary.com on IDEAL®

Using Human Data to Protect the Public's Health

Michael L. Dourson,*,[1] Melvin E. Andersen,† Linda S. Erdreich,‡ and Judith A. MacGregor§

*Toxicology Excellence for Risk Assessment, Cincinnati, Ohio 45223; †Colorado State University; ‡Exponent; and §Toxicology Consulting Services

Received February 26, 2001

The value of using human data in the assessment and management of risk is evaluated. Although the use of such data has a long and successful history with environmental contaminants and the development of drugs and commercial chemicals, recent deliberations within the Environmental Protection Agency (EPA) have questioned this practice in part. Specifically, we evaluate the degree to which reference doses (RfDs) and reference concentrations (RfCs) derived from human data on EPA's Integrated Risk Information System (IRIS) differ with RfDs and RfCs that we estimate from experimental animal data. We also use several minimal risk levels of the Agency for Toxic Substances and Disease Registry (ATSDR) and tolerable intakes of Health Canada in this comparison. Human-based RfDs are more than threefold lower than the corresponding animal-based RfDs for 29% of the comparisons. Human-based RfDs or RfCs are lower than corresponding animal-based RfDs or RfCs for 36% of the comparisons. Furthermore, for 10 of 48 possible comparisons, insufficient experimental animal data are readily available or data are inappropriate to estimate either RfDs or RfCs. We also discuss human pharmacokinetic data from volunteer studies and mechanistic studies with human tissues *in vitro* and demonstrate through a series of case discussions that utilization of such data is important when making decisions to protect exposed individuals. Moreover, physiologically based pharmacokinetic (PBPK) modeling evaluates critical information in assessing interindividual variability and identifying at-risk populations. Within the limits of our analysis, we conclude that the direct use and interpretation of human data, in conjunction with data gathered from experimental animals, are public health protective policies that should be encouraged.

Key Words: dose response; human; reference dose; reference concentration; risk; pharmacokinetics; pharmacodynamics; uncertainty factor.

INTRODUCTION

Is information from human studies the best way to judge the potential public health risk from chemicals in our environment? Should public health agencies strive to resolve the ethical questions and identify criteria to foster the conduct of human studies that might lead to better protection of the public's health? Should scientists ignore available human data that might suggest a lower or higher risk value? What is a risk value?

These issues have been a subject of much recent discussion (e.g., EPA, 2000a; Russo, 2000; SOT, 2000) and a topic of increased attention among both scientists and policy makers. Answers to these questions are complicated and not necessarily straightforward. Perhaps the easiest question to answer is the last because it covers a narrower part of the NAS (1983, 1994) risk assessment and risk management paradigm—that of hazard identification and dose–response assessment. Conceivably it should be the first question answered, since its response lays the foundation for the other questions involving more than the underlying science. We attempt to answer this question directly below. Other questions are discussed later.

What Is a Risk Value?

In its simplest form, a risk value is a given point on the dose–response curve associated with some probability of an outcome. In many cases, risk values are chosen to be associated with a level of zero or very small risk, usually referred to as "no appreciable risk." A common example of a risk value is a reference dose (RfD). A RfD is a point on the dose–response curve for a chemical of interest that is believed to be in the region of no adverse effect and is often used by risk managers to distinguish between the region of no adverse effect and the region of adverse effect. With either interpretation, however, the RfD does not distinguish between the region of *any* effect and that of no effect, because scientists often distinguish between a chemical's ability to cause an adverse effect and its ability to cause effects that are not considered adverse. For example, risk assessors often distinguish among adaptive, adverse,

[1]To whom correspondence and reprint requests should be addressed at Toxicology Excellence for Risk Assessment, 1757 Chase Avenue, Cincinnati, OH 45223. Fax: 513-542-7487. E-mail: Dourson@tera.org.

0273-2300/01 $35.00

compensatory, and critical effects.[2] In this process the concepts of severity of effect, homeostasis, and hormesis are often discussed.

Specifically, a RfD is defined as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime" (Barnes and Dourson, 1988). The reference concentration (RfC), where dose is expressed as a concentration, is similarly defined and applies to inhalation exposures (Jarabek, 1994, 1995). A measure or estimate of human exposure is often integrated with a risk value such as a RfD or RfC to develop a simple risk characterization, such as a maximum contaminant level goal (MCLG) in drinking water. This MCLG is then considered with other information in developing a risk management position, such as a maximum contaminant level (MCL). This MCL is enforceable and is designed to protect the public's health. EPA develops other risk characterizations and risk management decisions for other media. Such characterizations might involve more complex dose–response assessments and exposure assessments. Health organizations around the world use risk values and their associated exposure measures in similar fashion when conducting risk characterizations and arriving at risk management decisions.

In some cases, scientists postulate that a chemical may not have a distinguishable region of adverse effect and no adverse effect in the dose–response curve. In such cases, the adverse effect might occur at any dose, with more and more individuals being affected at greater doses (such as what might occur with cancer), or the adverse effect will not occur at any dose. With many chemicals this distinction is debated, because the scientific data are insufficient to provide certainty in conclusions in the area of the dose–response curve used for inference.

How Are Human Data Used?

Human data can be used in several ways in a hazard identification and dose–response assessment. For hazard identification, human data can be used alone to evaluate a finding or it may be used in concert with experimental animal data to provide weight-of-evidence that an observed association between exposure and response is actually caused by the exposure. In general, when used alone, human epidemiological data are insufficient evidence to strongly support causality (there are notable exceptions to this rule such as arsenic). In the case of human data associated with clinical studies or clinical interventions (such as for tamoxifen), the strength of the causal association is higher than with environmental epidemiological data. The main reasons for this difference pertain to limitations in the measurement of exposures in environmental epidemiological studies and the inability to control or include confounding variables that could also be associated with the observed toxicity.

In dose–response assessment, human data regarding the no-observed-adverse-effect level (NOAEL) can be used directly as the basis of a RfD or RfC. The presence of human data obviates the necessity of extrapolating from animals to humans; therefore, human studies, when available, are given first priority, with animal toxicity studies serving to complement them (Barnes and Dourson, 1988). However, using human data in this fashion requires that the human study be judged to be of at least comparable quality to an animal study that might be used to determine such a risk value. Moreover, the human study must conform to the highest standards associated with the conduct and evaluation of scientific data and include informed consent. Human data that are not directly useful as the basis of the NOAEL value can also be compared with animal data to determine the most appropriate interspecies uncertainty factor, rather than a default factor of 10 (Dourson *et al.*, 1996).

Human data can also be used as a guide to determine the appropriate toxicological end point to be considered for use in the hazard identification. In this regard, human case studies and incident reporting systems or other *in vivo* or *in vitro* experiments could be valuable when coupled with the more quantitative and better-controlled experimental animal toxicity studies. Used in this fashion, the human data can be seen to add mechanistic understanding of the critical effect determined from animals or to otherwise limit or bound the likely estimates of risk determined from the animal work in the dose–response assessment. They can also identify human effects that are not detected in animal studies, such as with the cardiac valvular defects

[2] Below are common definitions of types of effects. These effects are not always clear-cut categories, but often represent a continuum. Different individuals are expected to have different capacities for adaptive and compensatory effects.

- Adaptive effects are not considered to be adverse. They enhance an organism's performance as a whole and/or its ability to withstand a challenge. An increase in hepatic smooth endoplasmic reticulum is an example of an adaptive effect, if hepatic metabolism reduces the chemical's toxicity.
- Adverse effects are biochemical changes, functional impairments, or pathologic lesions that affect the performance of the whole organism or reduce an organism's ability to respond to additional environmental challenges (EPA, 2000b).
- Compensatory effects are not considered to be adverse. They maintain overall function without enhancement or significant cost. Increased respiration due to metabolic acidosis is an example of a compensatory effect.
- Critical effects are the first adverse effects or their known precursors that occur as dose rate increases (EPA, 2000b).
- Severity is the degree to which an effect changes and impairs the functional capacity of an organ system.

associated with the use of the drugs for weight loss (FDA, 1997).

What Are the Types of Human Data?

To date, the human data that have been used in risk assessments include a wide variety of types, based primarily on the different ways in which health data on humans can be obtained. Human data range from anecdotal case reports to systematically designed epidemiological studies of an exposed cohort. Epidemiological studies use several different approaches for collecting data, including surveillance, public health statistics, geographic correlation studies, and the cohort and case–control studies designed to identify associations and sometimes to support inferences about cause and effect. Human data also include experimental exposures of individuals; these are typically short-term studies that involve doses below a hypothesized threshold of adverse effect.

Epidemiological studies are routinely based on inadvertent exposures that may occur in the workplace, by unusual natural contamination, or as the aftermath of an accident such as an explosion or industrial release. However, deliberate exposure to humans has been used for centuries to test therapeutic procedures (Lee, 1980). Human studies are routinely used in drug development to evaluate the efficacy or safety of a therapeutic or diagnostic regimen. Clinical studies, or phase I clinical trials, are designed to identify a safe dose of a potential therapeutic or preventive agent. These studies are an intrinsic part of medicine, and methods for the design and statistical analysis of these studies are discussed in most statistical textbooks (Elwood, 1998).

The human experimental studies used for agents in the environment generally measure biochemical and/or physiological changes related to the anticipated adverse response in order to obtain quantitative information, usually for comparison with animal data. Criteria for both Phase I clinical trials and experimental studies in humans of environmental exposures include voluntary participation. Exposures to environmental chemicals are intended to produce minimal or no immediate adverse effects and no irreversible adverse effects (e.g., these studies usually examine an end point in the adaptive or compensatory response range). In the case of environmental exposures, studies are designed for multiple reasons such as to aid in understanding how exposures might be measured in a general population or to provide additional information for species comparisons and reduce uncertainty. In both cases, these studies are aimed at improving health. In the case of Phase I clinical trials for drugs, studies are designed to identify dosing levels that can be tolerated without any serious or unacceptable side effects and to serve as a guide for dose selection for future studies.

Approximately 7 of 8 potential drugs fail during clinical development and are subsequently not used (DeGeorge, 1999). For the 1 of 8 that are commercially developed, it is somewhat unlikely that a healthy volunteer would subsequently develop a need for the same pharmaceutical. In contrast, experimental studies for environmental contaminants have the potential for improving the risk estimates for chemicals for which the volunteers and the rest of the general public may more likely be exposed. Such improvement may have an indirect public health benefit. For example, the use of herbicides and pesticides may indirectly benefit health if the agents reduce organisms that are disease vectors, or increase accessibility to foods needed for a healthy diet.

For evaluation in this paper all RfDs and RfCs based on human data were selected from EPA's IRIS (EPA, 2000b). The human data that formed the basis of these RfDs and RfCs were of all types, for example: case reports of argyria from exposure to silver, epidemiological studies of populations exposed to natural arsenic or to methyl mercury from environmental contamination, a surveillance epidemiology study for methemoglobinemia from nitrate exposure, population studies of fluorosis, and experimental studies of aldicarb, barium, warfarin, and zinc.

Purpose of This Research

The purpose of this research is to compare established RfDs and RfCs based on human data with those we estimate based on experimental animal data, and to show the use of human toxicokinetic and toxicodynamic information for estimating noncancer and cancer risk. We also briefly discuss the use and interpretation of human data, in conjunction with data gathered from experimental animals, as a public health protective policy.

METHODS

Methods Used for Comparison of RfDs and RfCs

We chose to use the complete listing of noncancer risk values, that is RfDs and RfCs, based on human data as found in EPA's IRIS database (EPA, 2000b). RfDs and RfCs found in IRIS have gone through an extensive and rigorous development process, including internal peer review and unanimous acceptance within EPA. IRIS is not the only source of such information, of course (see for example www.tera.org/iter), but we used IRIS because it is convenient, reasonably robust, objective and respected (although many of the risk values are outdated). We compared these human-based RfDs and RfCs with RfDs and RfCs we estimate from readily available experimental animal data, mainly from IRIS, based on EPA dose–response assessment methods (Barnes and Dourson, 1988; Dourson, 1994; Jarabek, 1994, 1995; EPA, 1994). We chose not to do a similar comparison

for cancer risk values because of the added complexity of developing risk values from experimental animal data, although such work may be pursued in the future.

Our choice of appropriate experimental animal toxicity data to develop a RfD or RfC for comparison with an existing human value depended primarily on the availability of the experimental animal data. Confidence in the resulting comparison depends in part on the confidence one has in the human-based RfD or RfC (see Tables 1 and 2, which present confidence statements for risk values on IRIS), and on the relevance of the results in animals to the critical effect shown in humans. In descending order of importance, we selected experimental animal data to match:

- The dose–response curve of the critical effect in the human study (e.g., comparison of the dose–response curves of red blood cell cholinesterase (RBC) inhibition); or
- The benchmark dose (BMD), no-observed-adverse-effect level (NOAEL), or lowest-observed-adverse-effect level (LOAEL) of the critical effect in the human study (e.g., comparison of RBC cholinesterase inhibition NOAELs).

If matching data were not available, we then selected:

- A BMD, NOAEL or LOAEL of a closely related effect found in animals and compared it to the critical effect in humans (e.g., comparison of any clinical signs of cholinesterase inhibition); or
- The most sensitive effect found in animals and compared it to the critical effect in humans (e.g., comparison of cholinesterase inhibition with liver toxicity).

We recognized that pharmacokinetics and pharmacodynamics (discussed later) may impact such comparisons and conclusions drawn from these comparisons. Furthermore, the available experimental animal data may not include a species relevant to humans, and any such comparisons of these animal data with the human data may not be sufficiently predictive of effects in humans. Therefore, these comparisons of established human-based RfDs and RfCs with those we estimated from available animal data should be considered along with information on pharmacokinetics and pharmacodynamics in determining the usefulness of human data.

We developed animal-based RfDs and RfCs directly from the existing information on EPA's IRIS, and not from a thorough review of the original literature. In some cases, EPA's IRIS states an alternative RfD or RfC based on animal studies, and we used these alternative values instead of estimating them. Occasionally, we compared animal versus human risk values of ATSDR, EPA, and Health Canada as described on Toxicology Excellence for Risk Assessment's (*TERA*) International Toxicity Estimates for Risk (*ITER*) database (see *TERA*, 2000). Please note that the animal-based RfDs and RfCs that we derived have not undergone a rigorous peer review. Thus, the animal-based RfDs and RfCs that we provide should only be considered as interim, subject to change with additional data and/or analysis.

In all cases, we developed the experimental animal-based RfDs and RfCs assuming no relevant human data were available. Therefore, we used the default uncertainty factor of 10-fold (for RfDs) or 3-fold (for RfCs) for experimental animal to human extrapolation. Recent data and analysis by the EPA and others allow the use of specific human and animal toxicity, toxicokinetic and toxicodynamic data to affect the value of this and other uncertainty factors (Renwick, 1993; IPCS, 1994; Dourson, 1994; Dourson *et al.*, 1996; see also discussion below).

In the development of the animal-based RfDs and RfCs, we used the same database uncertainty factor and modifying factor as found in EPA's IRIS with one exception (the footnote for nitrite in Table 1 explains this exception). This decision is reasonable because the use of these factors, and the choice of other potential factors such as that recommended under the Food Quality Protection Act, reflects confidence in the overall database (EPA, 1999), which is the basis of both animal- and human-based RfDs and RfCs.

Methods for Pharmacokinetic Modeling

Making adjustments to animal results. Chemical risk assessments for cancer and noncancer end points are moving toward a common, harmonized methodology (Barton *et al.*, 1998). The basic steps in the approach are the establishment of a point of departure that may be a NOAEL, a LOAEL, or a BMD estimated from experimental data as described above. In the inhalation reference concentration methodology (EPA, 1994), the point of departure value is adjusted for differences in exposure duration to account for the fact that animals are exposed for less than 24 h per day while the exposure of interest for humans is continuous lifetime exposures. This duration-adjusted value is then corrected to take into account dosimetry differences expected between animals and human in order to provide a human equivalent concentration (HEC). These steps affect the numerator in the RfC equation. Several uncertainty factors are then applied to account for interspecies differences between test animals and humans and interindividual differences among humans. The HEC is divided by these uncertainty factors. Human pharmacokinetic and dosimetry data play potentially important roles in estimating the HEC and in assessing the magnitude of the uncertainty factors.

Mode of action and target tissue dose. The mode of action for a chemical entails the set of steps that are involved in causing toxicity following exposure to that particular chemical. Target tissue dose is the form of the chemical, i.e., parent compound, metabolite, peak

TABLE 1

Summary of U.S. EPA's RfDs on IRIS as of May 2000 Based on Human Data[1]

Chemical name (as on EPA's IRIS)	Specie/Type of study	NOAEL, LOAEL or BMD[2]	Critical effect(s)	Uncertainty factor[3]							RfD	RfD confidence	RfD ratio: Human to animal
				Total	H	A	L	S	D	MF			
Aldicarb	Human experimental gavage	0.01	Clinical signs of blood or plasma cholinesterase inhibition	10	10	1	1	1	1	1	1×10^{-3}	Medium	Either 1 (clinical signs) or 3 (plasma ChE)
	Rat developmental gavage	0.125	Clinical signs of cholinesterase inhibition	100	10	10	1	1	1		1×10^{-3}	Medium	
	Dog 52-week feeding	0.028[4]	Plasma cholinesterase inhibition	100	10	10	1	1	1		3×10^{-4}	Medium	
Arsenic, inorganic	Human epidemiology drinking water	0.0008	Skin lesions and possible vascular complications	3	3	1	1	1	1		3×10^{-4}	Medium	0.1
	Rat 13-week feeding[5]	2.6 (L)	Bladder hypertrophy and hyperplasia	1000	10	10	3	3	1		3×10^{-3}	Low	
Barium	Human experimental, epidemiological drinking water	0.21	Increased blood pressure	3	3	1	1	1	1		7×10^{-2}	Medium	0.4
	Rat chronic drinking water	46	Increased kidney weight	300	10	10	1	1	3		2×10^{-1}	Medium	
Baygon	Human experimental single dose	0.86 (L)	Mild cholinergic symptoms, RBC cholinesterase inhibition	100	10	1	10	1	1		4×10^{-3}	Medium	0.8
	Dog 12-month feeding	5 (L)	Cholinesterase inhibition	1000	10	10	10	1	1		5×10^{-3}	Medium	
Benzoic acid	Human anecdotal dietary exposure	4.4	No adverse effects observed	1	1	1	1	1	1		4	Medium	100^6
	Mouse chronic exposure	40 (L)	Decreased resistance to stress	1000	10	10	10	1	1		4×10^{-2}	Low	
Cadmium	Human chronic exposures from a variety of studies	0.005	Significant proteinuria	10	10	1	1	1	1		5×10^{-4}	High	N.A.
	N.A.[7]	N.A.	Insufficient information exists in the IRIS file to make any determination of an RfD								N.A.	N.A.	
Chlorpyrifos	Human experimental capsule	0.03	Plasma cholinesterase inhibition	10	10	1	1	1	1		3×10^{-3}	Medium	30
	Dog 2-year feeding	0.01	Dog plasma and RBC cholinesterase inhibition	100	10	10	1	1	1		1×10^{-4}	Medium	
4,6-Dinitro-o-cyclohexyl-phenol	Human anecdotal clinical therapy	3.0 (L)[8]	Cataract formation	1000	10	1	10	10	1		2×10^{-3}	Low	Either 0.03 (cataract) or 0.07 (growth depression & swelling)
	Rat 6-month feeding	64 averaged	Cataract formation[9]	1000	10	10	1	10	1		6×10^{-3}	Low	
	Rat 6-month feeding	32 averaged	Growth rate depression, cloudy swelling of liver cells	1000	10	10	1	10	1		3×10^{-3}	Low	

	Dog 90-day oral exposure	0.06 (L)	Plasma cholinesterase inhibition	1000	10	10	10	1	1				
Fluorine (soluble fluorida)	Human epidemiology	0.06	Objectionable dental fluorosis	1	1	1	1	1	1	6×10^{-3}	High	N.A.
	N.A.	N.A.	Insufficient information exists in the IRIS file to make any determination of RfD							N.A.	N.A.	
Malathion	Human experimental feeding	0.23	Erythrocyte cholinesterase inhibition	10	10	1	1	1	1	2×10^{-2}	Medium	0.4
	Rat 2-year feeding	5	Decreased brain cholinesterase and decreased body weight	100	10	10	1	1	1	5×10^{-3}	Medium	
Manganese	Human data of several types	0.14	No LOAEL given, CNS effects appear to occur at higher doses	1	1	1	1	1	1	1.4×10^{-2}	Medium	N.A.
	N.A.	N.A.	IRIS states that human data are superior to any data obtained from animal toxicity studies as the basis of an RfD, since the physiologic requirements for manganese vary among species							N.A.	N.A.	
Methyl mercury	Human epidemiological poisoning	0.0011 (B)	Infant developmental neurological abnormalities	10	3	1	1	1	3	1×10^{-4}	Medium	5
	Rat developmental gavage and 26-month feeding study	0.005	Decrease in operant behavior performance, reduced body weight gains, minimal clinical signs of neurotoxicity, kidney damage	300	10	10	1	1	3	2×10^{-5}	Medium	
Molybdenum	Human epidemiological dietary	0.14 (L)	Increased uric acid	30	3	1	10	1	1	6×10^{-3}	Medium	2
	Rat 13-week feeding	2.5 (L)	Retarded weight gain	1000	10	10	3	3	1	3×10^{-3}	Low	
Nitrate	Human epidemiology surveys	1.6	Early clinical signs of methemoglobinemia <10%	1	1	1	1	1	1	1.6	High	5
	Rat 24-month drinking water	20[11]	Dilated bronchi, fibrosis, and emphysema	100	10	10	1	1	1	3×10^{-1}	Medium	

											× 10^{-1}	Medium	N.A.
Zinc and compounds	Human experimental diet supplement	59.7 (L)	Decrease in erythrocyte superoxide dismutase concentration in adults								N.A.	N.A.	
	N.A.	N.A.	Insufficient information exists in the IRIS file to make any determination of RfD										

[1] All data from which we estimate animal-based RfDs are taken from EPA's IRIS unless otherwise stated. Judgments of confidence levels for animal-based risk values were based on M. Dourson's experience with the RfD/RfC Work Group of EPA.

[2] All values are in mg/kg-day and are NOAELs unless otherwise stated: (L), LOAEL; (B), benchmark dose (BMD).

[3] Uncertainty factors are H, average human to sensitive human; A, animal to human; L, LOAEL to NOAEL; S, subchronic exposure to chronic; D, database insufficiency; MF, modifying factor to account for uncertainties not covered by the traditional factors. Note that for this exercise, the D and MF factors were considered to be the same between the animal-based RfD and the human-based RfD, since they originated from the same database with one exception (nitrite) since information on IRIS allowed a difference. These [illegible] evaluation of newer toxicity data not on IRIS.

[illegible] both low dose were consider as NOAELs; if they are

TABLE 1—*Continued*

Chemical name (as on EPA's IRIS)	Specie/Type of study	NOAEL, LOAEL or BMD[2]	Critical effect(s)	Uncertainty factor[3]							RfD	RfD confidence	RfD ratio: Human to animal
				Total	H	A	L	S	D	MF			
Nitrite	Human epidemiology surveys	1.0[19]	Early clinical signs of methemoglobinemia/ <10%	1	1	1	1			10	1×10^{-1}	High	5
	Rat 24-month drinking water	2	Dilated bronchi, fibrosis, and emphysema	100	10	10	1				2×10^{-3}	Medium	
Pirimiphos-methyl	Human 56-day experimental feeding	0.25	Transient plasma cholinesterase inhibition	25	10	1	2.5				1×10^{-2}	High	Either 2 (rat) or 20 (dog)
	Rat 2-year feeding	0.5	Plasma cholinesterase inhibition	100	10	10	1				5×10^{-3}	High	
	Dog 2-year feeding	0.5(L)	Brain cholinesterase inhibition	1000	10	10	10				5×10^{-4}	Medium	
Selenium and compounds	Human food and soil epidemiology	0.015	Clinical selenosis	3	3	1	1				5×10^{-3}	High	6
	Rat developmental toxicity	0.075	50% reduction in number of young reared	100	10	10	1				5×10^{-4}	High	
Silver	Human anecdotal studies	0.014	Argyria	3	3	1	1				5×10^{-3}	Low	0.2
	Rat 218-day drinking water exposure	69 (L)	Ventricular hypertrophy	000	10	10	10				3×10^{-3}	Low	
1,1,2-Trichloro-1,2,2-trifluoro-ethane	Human occupational exposure	273	Psychomotor impairment	10	10		1				3×10^{1}	Low	N.A.
	N.A.	N.A.	Insufficient information exists in the IRIS file to make any determination of RfD								N.A.	N.A.	
Warfarin	Human experimental [illegible]	0.029	Increased prothrombin time	100	10		10				3×10^{-4}	Low	N.A.
	N.A.	N.A.	IRIS states "Because of								N.A.	N.A.	

concentrations, net exposures as area under the concentration curves, that is believed to be most closely associated with the toxic effects. Any narrative describing the mode of action of a compound should also convey the form of the chemical believed to be responsible for initiating the cascade of steps leading to the toxic responses. Similarly, extrapolation between species should be conducted using a dose metric that reflects this understanding of the mode of action of the compound.

For example, a mode of action statement for vinyl chloride would be: tumors associated with vinyl chloride are caused by mutational effects arising from the reaction of epoxide metabolites with DNA resulting in increases in the mutational frequency in specific cells. The dose metric for this mode of action would be a measure of the net tissue exposure of the epoxide metabolites (EPA, 2000b). For chloroform, the mode of action statement would read: tumors in the liver and kidney induced by chloroform arise due to mutations during recurrent episodes of cytotoxicity and cell proliferation associated with metabolism of chloroform to phosgene in cells with high CYP 2E1 activity. Here the dose metric would be related to peak rates of metabolism of chloroform in liver and in kidney cortex (ILSI, 1997).

Pharmacokinetic and dosimetry data in risk assessment. Several advances in dose–response assessment have occurred over the past 20 years due to increased emphasis on understanding modes of action and on determining the major biological determinants that contribute to pharmacokinetic behavior in animals and humans. Before 1980, it was common to simply collect pharmacokinetic data and analyze it empirically with mathematical models to evaluate the correspondence of the data with specific compartmental models. Sometimes the data were not analyzed at all. A difficulty with these compartmental approaches was in extrapolation of the results to important untested situations. Even when impressive fits to animal data were obtained, how confident could we be that the compounds would have similar kinetic behavior in humans? If human data were actually obtained from volunteers, how confident could we be that the data obtained from a small group of healthy individuals were representative of pharmacokinetic behaviors expected in a larger human population? These two questions led to increased emphasis on development of physiologically based pharmacokinetic (PBPK) models in which the organism is described realistically in terms of anatomy, physiology, biochemical parameters of distribution, and the physical-chemical characteristics of the test compound (Gerlowski and Jain, 1983). These particular models are more amenable to extrapolation from test animals to humans and are also amenable to establishing the importance of variability within the human population by Monte Carlo methods.

RESULTS

Comparison of Human- and Experimental Animal-Based RfDs and RfCs

Table 1 shows a comparison of all RfDs based on human data as found on IRIS (EPA, 2000b) or for several chemicals on *ITER* (*TERA*, 2000), and those we estimate from experimental animal data found on IRIS using the criteria defined above. For 36% (8 of 22 comparisons), the human- and animal-based RfDs are comparable, that is within the limits of their corresponding precision.[3] For 23% (5 of 22 comparisons), the RfDs based on human data are lower than the corresponding RfDs based on animal data. For 41% (9 of 22 comparisons), RfDs based on animal data are lower than those based on human data. An animal-based RfD could not be estimated in 6 of 28 possible comparisons, since animal information was judged to be either insufficient or irrelevant.

Table 2 shows a comparison of all RfCs based on human data as found on IRIS (EPA, 2000b) or for several chemicals on *ITER* (*TERA*, 2000), and those we estimate from experimental animal data found on IRIS using criteria defined above. For 45% (5 of 11 comparisons), the RfCs are comparable, that is within the limits of their corresponding precision.[3] In no cases were the RfCs based on human data lower than the corresponding RfCs based on animal data within the limits of precision being assumed. For 55% (6 of 11 comparisons), RfCs based on animal data are lower than those based on human data. An animal-based RfC could not be estimated for 4 of 15 times, since animal information was judged to be either insufficient or irrelevant.

Figure 1 shows a frequency plot of human- to experimental animal-based RfD or RfC ratios from Tables 1 and 2.

Differences in the ratios of the human to the experimental animal RfD or RfC can also be shown as the number that were above or below a value of 1 without regards to any considerations of precision. Here values below 1 indicate that human data resulted in a lower RfD or RfC than animal data. For RfDs this frequency is 9 of 22 (or 41%). For RfCs this frequency is 3 of 11 (or 27%). Collectively, this frequency is 12 of 33 (or 36%). This percentage represents the number of times a human-based RfD or RfC was lower than a corresponding animal-based RfD or RfC.

[3] These frequency values are based on ratios that fall within a 10-fold range of each other, for example 0.3 mg/kg-day ≤ RfD ≤ 0.3 mg/kg-day. The use of such a range is consistent with the definition of RfDs and RfCs in that "uncertainty spans perhaps an order of magnitude" and thus their expected level of precision. However, the precision of risk values has never been explicitly addressed in EPA risk values (see Faber and Dourson, 1998, for more discussion of this), and therefore the range we use here is only for demonstration. Other equally valid ranges may be determined.

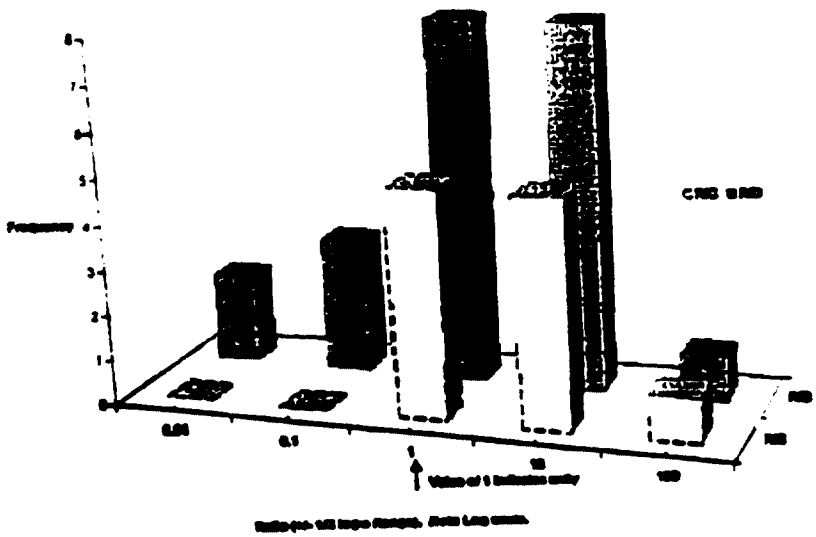


FIG. 1. Frequency of human- to animal-based RfD and RfC ratio from Tables 1 and 2. Ranges defined by logarithmic midpoints (e.g., $0.3 < 1 \leq 3$). Value of 1 indicates that animal-based and human-based risk values are the same.

Table 3 shows human to animal RfD ratios from Table 1, where experimental or anecdotal clinical human data formed the basis of EPA's assessment. The purpose of this subset analysis is to determine whether different kinds of human data allow the development of different conclusions. Eight of 15 comparisons (53%) of human to animal RfDs are less than 1. If anecdotal clinical data are excluded from these comparisons, then 3 of 10 comparisons (30%) of experimental human-based to animal-based RfDs are less than 1. Unfortunately too few comparisons exist in order to make any definitive conclusions on the relative proportions of these ratios amongst the different types of human data as described in the introduction. However, these percentages of ratios less than 1 found in Table 3 are not dissimilar from the percentage of ratios with the overall RfD database of 41% (found in Tables 1 and 2).

It is of interest to study the reasons why certain risk values could not be based on animal data. This occurred with a frequency of 6 of 28 (or 21%) for RfDs and 4 of 15 (or 27%) for RfCs. Table 4 shows the stated reasons derived from Tables 1 and 2. For 40%, the stated reason is a scientific judgment that the animal data are not relevant to the development of a risk value for humans as further explained in individual chemical files on IRIS (EPA, 2000b). For 60%, the animal data was not sufficiently described on EPA's IRIS to develop a risk value.

Comparison of Human and Experimental Animal Pharmacokinetics

Human data for risk assessment purposes include *in vitro* determinations of biochemical constants for metabolism and tissue partition coefficients, limited pharmacokinetic studies in specific human populations, and mechanistic studies using human tissues or human cells *in vitro*. The emphasis in this section is on the use of kinetic data and *in vitro* methods for assessing biological determinants of kinetics in human tissues. A Contemporary Concepts in Toxicology Workshop under the auspices of the Society of Toxicology (SOT) Task Force to Improve the Scientific Basis of Risk Assessment was held in September 1999. The report of the workshop outlining the uses of human tissues in risk assessment is in press (MacGregor *et al.*, 2000). This paper provides a larger perspective on use of human tissues for mechanistic studies.

We describe a series of examples to illustrate the use of human pharmacokinetic data in risk assessment.

Dichloromethane

Human equivalent concentrations. Occupational toxicology has historically featured the use of human volunteers for assessing the pharmacokinetics of industrial chemicals. Long before human testing was undertaken, the occupational importance and history of the compound's usage in industrial environments was established. In general, exposure standards had been established and the human exposures were conducted at exposure levels at or below existing Threshold Limit Values or equivalent occupational standards. Work with human volunteers in the 1970's established the conversion of dichloromethane (DCM; methylene chloride) to carbon monoxide and the production of relatively high levels of carboxyhemoglobin (HbCO)—from 5 to 20%—following high level exposures to this solvent. The analytical methods for measuring most

TABLE 2
Summary of U.S. EPA's RfCs on IRIS as of May 2000[1]

Chemical name (as on EPA's IRIS)	Specie/Type of study	Human Equivalent NOAEL, LOAEL, or BMD[2]	Critical effect(s)	Uncertainty factor[3]							RfC	RfC confidence	RfC ratio: Human to animal
				Total	H	A	L	S	D	MF			
Ammonia	Human occupational	2.3	Lack of evidence of decreased pulmonary function or changes in subjective symptomatology	30	10	1	1	1	3		1×10^{-1}	Medium	20
	Rat subchronic inhalation	1.9 (L)	Increased severity of rhinitis and pneumonia with respiratory lesions	300	10	3	3	1[4]	3		6×10^{-3}	Medium	
Beryllium	Human occupational and community exposure	0.0002 (L)	Beryllium sensitization and progression to chronic beryllium disease (CBD)	10	1	1	3	3	1		2×10^{-4}	Medium	N.A.
	N.A.[5]	N.A.	No laboratory animal model fully mimics all features of human CBD								N.A.	N.A.	
Bromomethane	Human occupational	2.2 (L)[6]	Neurological effects	100	10	1	10	1	1		3×10^{-3}	N.A.	4
	Rat 28-month inhalation	6.46 (L)	Degenerative and proliferative lesions of the olfactory epithelium of the nasal cavity	100	10	3	3	1	1		5×10^{-3}	High	
Carbon disulfide	Human occupational	19.7 (B)	Peripheral nervous system dysfunction	30	3	1	1	3	3		7×10^{-1}	Medium	8
	Rat 90-day inhalation	27	Peripheral nervous system dysfunction	300	3	3	1	10	3		9×10^{-2}	Medium	
Chromium (acid mists and aerosols)	Human subchronic occupational	0.000714 (L)	Nasal septum atrophy	90	10	1	3		1		8×10^{-4}	Low	N.A.
	N.A.	N.A.	Experimental animal studies have not reported on nasal mucosal effects following inhalation exposures								N.A.	N.A.	
N,N-Dimethylformamide	Human occupational	7.9 (L)	Digestive disturbance and minimal hepatic changes suggest liver effects	300	10	1	3		3		3×10^{-2}	Medium	4
	Rat 4-week inhalation	35 (L)	Hepatic cell changes	3000	10	3	10^{2}				3×10^{-2}	Medium	
n-Hexane	Human inhalation epidemiology	72 (L)	Neurotoxicity; electrophysiological alterations	300	10	1	10				2×10^{-1}	Medium	0.5
	Mouse 90-day inhalation	88	Epithelial lesions in the nasal cavity	100	10	3					4×10^{-1}	Medium	

Hydrogen cyanide	Human occupational	2.5 (L)	CNS symptoms and thyroid effects	1000	10	1	10	3	3	1	3×10^{-3}	Low	N.A.		
	N.A.	N.A.	Insufficient information exists in the IRIS file to make any determination of RfC								N.A.	N.A.			
Manganese	Human occupation exposure	0.05	Impairment of neurobehavioral function		1000	10	1	10	3	3	1	5×10^{-5}	Medium	N.A.	
	N.A.	N.A.	IRIS states that animal toxicity data qualitatively support the human studies used as a basis of the RfC; quantified comparisons were not provided									N.A.	N.A.		
Mercury, elemental	Human occupational	0.009 (L)	Hand tremor; increases in memory disturbances; slight subjective and objective evidence of autonomic dysfunction		30	3	1	3	1	3	1	3×10^{-4}	Medium	0.4	
	Rat 72-week inhalation	0.07	No histopathological evidence of respiratory damage; higher doses caused developmental toxicity in a different study		100	10	3	1	1	3	1	7×10^{-4}	Low		
Styrene	Human occupational	34	CNS effects		30	3	1	1	3	3	1	1	Medium	50	
	Mouse subchronic inhalation	74 (L)	Bronchiolar regeneration, olfactory metaplasia and degeneration, increased lung weight, increased epithelial hyperplasia of the forestomach		3000	10	3	10	3	3	1	2×10^{-3}	Medium		
Tetrachloroethylene	Human occupational	24 (L)[9]	Increased reaction times to simple neurological tests		100	10	1	10	1	1	N.A.	2×10^{-16}	N.A.	0.6	
	Mouse 103-week inhalation	353 (L)[11]	Reduced survival (in males), hepatotoxicity (males), lung congestion and nephrotoxicity (males and females)		1000	10	10	10	1	1	N.A.	3.6×10^{-19}	N.A.		
Toluene	Human occupational	119 (L)	Neurological effects		300	10	1	10	1	3	1	4×10^{-1}	Medium	5	
	Rat 2-year inhalation	79 (L)	Degeneration of nasal epithelium		1000	10	3	10	1	3	1	8×10^{-2}	Medium		
Toluene diisocyanate mixture (TDI)	Human occupational	0.002	Chronic lung function decline		30	10	1	1	3	1	1	7×10^{-6}	Medium	2	
	Rat chronic inhalation	0.01 (L)	Necrotic rhinitis with epithelial atrophy, metaplasia, and inflammation		300	10	3	10	1	1	1	3×10^{-5}	Medium		

TABLE 2–Continued

Chemical name (as on EPA's IRIS)	Specie/Type of study	Human Equivalent NOAEL, LOAEL, or BMD[2]	Critical effect(s)	Uncertainty factor[3]							RfC	RfC confidence	RfC ratio: Human to animal
				Total	H	A	L	S	D	MF			
Xylenes	Human occupational	60.76 (L)[9]	Subjective symptoms	100	10	1	10	1	1	N.A.	6×10^{-1} [10]	N.A.	3
	Rat inhalation developmental toxicity	177 (L)[11]	Fetal toxicity	1000	10	10	10	1	1	N.A.	1.8×10^{-1}	N.A.	

[1] All data from which we estimate animal-based RfCs are taken from EPA's IRIS unless otherwise stated. Judgments of confidence levels for animal-based risk values were based on M. Dourson's experience with the RfD/RfC Work Group of EPA.

[2] All values are human equivalent concentration in mg/m^3 and are NOAELs unless otherwise stated: (L), LOAEL; (B), benchmark concentration (BMC).

[3] Uncertainty factors are H, average human to sensitive human; A, animal to human; L, LOAEL to NOAEL; S, subchronic exposure to chronic; D, database insufficiency; MF, modifying factor to account for uncertainties not covered by the traditional factors. Note that for this exercise, the D and MF factors were considered to be the same between the animal-based RfD and the human-based RfD, since they originated from the same database. These factors may not be the same upon reevaluation of newer toxicity data not on IRIS.

[4] The value of this subchronic to chronic uncertainty factor is 1; it is subsumed in the description of the uncertainty factor for database deficiencies as per IRIS.

[5] N.A., not applicable.

[6] Value is from ATSDR and the resulting risk value is a minimal risk level (MRL). Some differences exist among methods to estimate these risk values among EPA and ATSDR. Please see www.tera.org/iter/methods. Specific values of ATSDR and EPA can be found at www.tera.org/iter under "bromomethane."

[7] An evaluation of the original study within the overall database may allow a reduction in this factor to a value of 3.

[8] Specific values of ATSDR and Health Canada can be found at www.tera.org/iter under "tetrachloroethylene."

[9] Value is from ATSDR and the resulting risk value is a minimal risk level (MRL). Some differences exist among methods to estimate these risk values among EPA, ATSDR, and Health Canada. Please see www.tera.org/iter/methods

[10] Specific values of ATSDR and Health Canada can be found at www.tera.org/iter under "xylenes."

[11] Value is from Health Canada and the resulting risk value is a tolerable concentration (TC). Some differences exist among methods to estimate these risk values among EPA and ATSDR. Please see www.tera.org/iter/methods.

TABLE 3

Summary RfDs from Table 1 Based on Experimental or Clinical Human Data

Chemical name (as on EPA's IRIS)	Species/Type of study	Critical effect(s)	RfD	ratio: Human to animal
Aldicarb	Human experimental gavage	Clinical signs of cholinesterase inhibition, plasma cholinesterase inhibition	1×10^{-3}	Either 1 (clinical signs) or 3 (plasma ChE)
	Rat developmental gavage	Clinical signs of cholinesterase inhibition	1×10^{-3}	
	Dog 52-week feeding	Plasma cholinesterase inhibition	3×10^{-4}	
Barium	Human experimental, epidemiological drinking water	Increased blood pressure	7×10^{-2}	0.4
	Rat chronic drinking water	Increased kidney weight	2×10^{-1}	
Baygon	Human experimental single dose	Mild cholinergic symptoms, RBC cholinesterase inhibition	4×10^{-3}	0.8
	Dog 12-month feeding	Cholinesterase inhibition	5×10^{-3}	
Chlorpyrifos	Human experimental capsule	Plasma cholinesterase inhibition	3×10^{-3}	30
	Dog 2-year feeding	Plasma and RBC cholinesterase inhibition	1×10^{-4}	
4,6-Dinitro-o-cyclohexyl phenol	Human anecdotal clinical therapy	Cataract formation	3×10^{-3}	Either 0.03 (cataract) or 0.07 (growth) depression and swelling)
	Rat 6-month feeding	Cataract formation	6×10^{-5}	
	Rat 6-month feeding	Growth rate depression, cloudy swelling of liver cells	3×10^{-5}	
2,4-Dinitrophenol	Human anecdotal clinical therapy	Cataract formation	2×10^{-3}	Either 0.02 (cataract) or 0.4 (growth depression and swelling)
	Rat 6-month feeding	Cataract formation	1×10^{-3}	
	Rat 6-month feeding	Growth rate depression, cloudy swelling of liver cells	5×10^{-5}	
Ethephon	Human experimental oral exposure	Plasma cholinesterase inhibition	5×10^{-3}	6
	Dog 2-year feeding	Plasma cholinesterase inhibition	8×10^{-4}	
Ethion	Human experimental short term	Plasma cholinesterase inhibition	5×10^{-4}	8
	Dog 90-day oral exposure	Plasma cholinesterase inhibition	6×10^{-5}	
Malathion	Human experimental feeding	Erythrocyte cholinesterase depression	2×10^{-2}	0.4
	Rat 2-year feeding	Decreased brain cholinesterase and decreased body weight	5×10^{-2}	
Pirimiphos-methyl	Human 56-day experimental feeding	Transient plasma cholinesterase inhibition	1×10^{-3}	Either 2 (rat) or 20 (dog)
	Rat 2-year feeding	Plasma cholinesterase inhibition	5×10^{-3}	
	Dog 2-year feeding	Brain cholinesterase inhibition	5×10^{-4}	
Silver	Human anecdotal studies	Argyria	5×10^{-3}	0.2
	Rat 218-day drinking water exposure	Ventricular hypertrophy	3×10^{-3}	
	Human experimental	Increased prothrombin time	3×10^{-4}	
Warfarin	Inappropriate	IRIS states "Because of marked differences in the susceptibility of different species to the effects of warfarin, it would be inappropriate to derive an RfD from studies on lower animals"	N.A.	N.A.
		Decrease in erythrocyte superoxide dismutase concentration in adults	3×10^{-1}	N.A.
Zinc and compounds	Human experimental diet supplement N.A.	Insufficient information exists in the IRIS file to make any determination of RfD	N.A.	

compounds in blood and excreta were new and many had only moderate sensitivity. The work with DCM established the exposure concentrations associated with specific increases in HbCO and led to strategies for controlling DCM that insured no more than a 5% increase in blood HbCO. This early work with DCM, while quantitative, provided simple mathematical relationships to correlate specific exposures with increased HbCO; they did not really allow prediction of these values from knowledge of human metabolism, physiology, and activity levels.

In the 1980s, DCM was found to be carcinogenic in mice, shifting the end point from HbCO to the possibility that DCM might cause cancer in exposed individuals. A risk assessment for DCM was proposed, based on a PBPK model, that estimated the tissue exposures in lung and liver to metabolites of DCM (Andersen *et al.*, 1987). A variety of data indicated that the carcinogenicity in mice was most likely associated with metabolites formed by conjugation of DCM with glutathione, catalyzed by glutathione *S*-transferase (GST). This metabolic clearance pathway competes with a higher affinity, though lower capacity oxidation of DCM by cytochrome P450. The isozyme involved is now recognized to be CYP2E1. The dose metric used for analysis in the region of observation was the integrated production of the glutathione conjugate per volume tissue per day. This same dose metric was estimated for humans by using a PBPK model that included physiological parameters for humans and kinetic constants for the glutathione-*S*-transferase enzyme in lung and liver for both the mouse and the human. Using model substrates, activities for the human liver and lung enzymes were estimated in studies using microsomes obtained from accident victim's tissues. Later work established the activities of these enzymes toward DCM itself (Reitz *et al.*, 1989).

Controlled pharmacokinetic studies had been conducted in human volunteers using several different concentrations of DCM (Andersen *et al.*, 1991). These studies were evaluated with a PBPK model to assess the consistency of predictions based on scaling the rodent PBPK model to predict actual human data. The earlier risk assessment had simply used a model with human parameters to make predictions of the dose metrics. With moderate refinements to the portion of the model describing carbon monoxide distribution after its formation by DCM oxidation, the model predicted the blood and exhaled air time-course for DCM. For CO, the model adequately predicted blood HbCO and exhaled CO. The ability to match concentrations of DCM, HbCO, and CO in humans provides confidence that the scale-up from rats to humans is feasible. These results collectively and individually provide evidence for the correction in the numerator of the RfC, for example, that which is required for developing a human equivalent concentration. The dose metric used is the amount of HbCO formed for an occupational concern for carboxyhemoglobin or the amount metabolized in lung or liver by the glutathione-*S*- transferase reactions. This latter dose metric is estimated from an accurate prediction of the blood concentrations of DCM and the enzyme activities in the target tissues. These PBPK models allow estimation of the human exposure concentrations that are required to provide a tissue dose similar to that associated with the point of departure concentration in the test animal.

Human variability. The denominator of the RfC and RfD includes uncertainty factors for interspecies and intraindividual differences. The RfC methodology (EPA, 1994) indicates that the interspecies factor can be reduced when compound specific kinetic data are used to derive the human equivalent concentration. A second application of these kinetic models is to estimate the impact of variability in physiology, metabolism, etc. in pharmacokinetic variability within the human population. For this application, ranges of model parameters, such as breathing and blood flow rates, body composition, and metabolic parameters, are introduced into the model specification. The PBPK model is run multiple times during which the parameters are selected from these distributions by a sampling algorithm. The resultant output is a distribution for target tissue dose expected for a diverse population at the specified exposure concentration. By assessing the variability in this distribution of tissue doses, it becomes possible to decide if the factor of 10 for intraindividual differences is adequate or if it needs to be adjusted. Examples of use of Monte Carlo sampling of parameter distributions to assess tissue dose with DCM have focussed on standard setting for the workplace (Thomas *et al.*, 1998) and for environmental exposures (Clewell, 1996).

The work with DCM provides a template for applications of human data in risk assessment based on toxicity results in animals. Mechanistic studies usually set the foundation for assessing the dose metric that is important to estimate as a measure of tissue dose. The PBPK model indicates the important parameters that determine the dose of active forms of the compound at target tissues. Studies with human tissues, coupled with knowledge of human physiology/anatomy, provide a method to estimate human tissue doses of active compounds and a method to derive the HEC. Focused, limited, human-volunteer studies, develop *in vivo* data that allows refinement and validation of the predictions of the human PBPK model. The completed PBPK description lends itself to a refined, quantitative analysis of variability in pharmacokinetic behavior in the human population. This paradigm for use of human studies would be applicable to RfC, RfD or cancer assessments for various end points. In contrast

to the state-of-the-art in analytical chemistry in the 1970s, many of the pharmacokinetic studies in humans can now be conducted at much lower, almost tracer (or trace) levels of contaminants mitigating concerns about possible adverse effects of compounds in the human volunteers.

Vinyl Chloride

Pharmacokinetic (PK) modeling plays an increasingly accepted role in many of the efforts in the new IRIS Pilot project activities to integrate the risk assessment process for specific compounds. Vinyl chloride (VC) documentation has been completed within the last year (EPA, 2000b). The critical end points with VC are liver toxicity and liver cancer—hemangiosarcoma. VC is an animal and human carcinogen with strong site-concordance between species. Mechanistic work has firmly established a central role for an epoxide, metabolite in causing DNA adducts, mutations, and tumors. Pharmacokinetic and disposition studies have been conducted in multiple species of laboratory animals and limited pharmacokinetic uptake studies were conducted with human volunteers at low concentrations. The IRIS document with VC includes a PBPK model to assess the consistency in dosimetry between animals and humans, and provides methods for extrapolating across dose routes and between species. The human data provides a test of model predictions and reassurance that the standards set based on these modal estimates of dose are likely to be sound.

Inhaled Acids and Esters

A wide variety of organic acids and esters have recently been associated with degeneration and toxicity in the nasal olfactory epithelium in rats and mice. It was unclear whether these compounds would have similar effects in humans. Within the past two to three years, PBPK models have been completed and published for several of these compounds—vinyl acetate (Plowchalk *et al.*, 1997), acrylic acid (Frederick *et al.*, 1998), and methyl methacrylate (Andersen *et al.*, 1999). Dosimetry model development with these compounds has included evaluation of uptake from the rodent airstream, parameterization of nasal models for airflow and tissue uptake, and measurement of metabolizing enzymes in epithelial tissues throughout the nose. These dosimetry models predict differences between humans and rodents and support estimation of HECs for these compounds. A workshop was held in Research Triangle Park, North Carolina, in February 1998. Participants discussed the utility of these dosimetry models for nasal dosimetry and risk assessment and continuing data needs. A major continuing data need enumerated was for human studies of scrubbing of compounds from the nasal airstream using specific breathing patterns and sampling strategies (Andersen and Jarabek, 2000). The validation of existing models by selective, carefully designed human studies was recognized as an important research priority.

Boric Acid

The most sensitive end point with boric acid in laboratory animals is developmental toxicity in the offspring of Sprague–Dawley rats (Dourson *et al.*, 1998). This inorganic acid has fairly straightforward pharmacokinetic behavior. It is not metabolized to any appreciable extent; it is primarily excreted into the urine via the kidneys; and it does not accumulate anywhere in the body. The main issue in assessing the uncertainty factors for this compound is estimation of the net tissue exposure to fetuses in rats and any differences in exposure for equivalent doses in humans. General arguments can be offered regarding the expected kinetic behavior. For instance, the volume of distribution should follow body weight (or at least lean body weight) and renal clearance should follow body weight raised to the 2/3 power (see, for example, NRC, 1986). These are theoretical arguments for generic compounds. It would be best to estimate these differences by direct determination of boric acid clearance studies in pregnant and nonpregnant females.

These renal clearance studies have recently been conducted by the University of California, Irvine (Vaziri *et al.*, 2000). Murray and Andersen (2000) provide a preliminary outline of the results of these studies, including relative areas under the blood curve and the variability observed in renal boric acid clearance in both rats and women. These studies provide data to clearly obtain compound-specific adjustment factors to replace default or rule of thumb interspecies adjustments. The work focussed attention on the need to define a dose metric for interspecies adjustment. Two possibilities are peak maternal blood levels or net fetal exposure during the critical period, which should be proportional to net area under the boric acid blood curve in maternal plasma.

Criteria Pollutants

Chemicals with extensive history of controlled human experimentation are the criteria pollutants, including ozone, sulfur dioxide, nitrogen oxides, and carbon monoxide. These byproducts of commerce and of the internal combustion engines that fuel our technical society achieve airborne concentrations quite close to frank effect levels. Human studies of dosimetry, the amounts retained in the lungs, and pulmonary function in healthy and in compromised individuals have been important in setting acceptable ambient levels for these compounds that strike a balance between safety and continuing economic activity.

Organophosphates (OPs)

In adults, at least, the main risks posed from acute exposures to OPs are associated with inhibition of tissue cholinesterases and impaired cholinergic transmission. For the thiophosphorate compounds, toxicity is complexly related to activation to the active oxon, a process that has to compete with metabolism, including hydrolysis to inactive products. How do these various processes work together in target pest species or in inadvertant target species that may be exposed to these compounds?

PBPK models have been developed for organophosphate compounds in order to integrate knowledge of various pathways in both causing toxicity or in inactivating the compounds before they can exert their biological effects (Gearhart *et al.*, 1990). The possibility exists to collect *in vitro* data with human tissues, blood, etc., to assess kinetic constants for various pathways and develop a predictive model for production and distribution of the oxon. The time course of the oxon in blood and tissues would be directly related to inhibition of the target macromolecules. These predictive models should be validated by limited studies in human volunteers. With current analytical methods, these studies can be done at dosages where there are minimal changes in any of the esterase activities in the body. The main goal of such work is not simply to assess doses that cause some *minimal* change in blood or plasma cholinesterase. Instead, they fulfill multiple objectives by assessing the major biological determinants of the kinetics of parent compound and oxon. As with all human studies, doses of these materials have to be carefully selected and the dosing closely supervised by a physician. However, human data are critical for making sound judgements about the use of these compounds, insuring protection of all exposed individuals, and avoiding overreliance of default approaches for animal to human extrapolation for such a widely used group of compounds.

With this information, it is possible to examine expected differences among individuals associated with metabolic polymorphisms and to ascertain if the pharmacokinetics seen in other species are expected in humans. In addition, these mechanistic PBPK models can explore whether there may be specific populations—aged, youth, or compromised individuals—who may be at greater risk. This evaluation is conducted by providing distributions of critical parameters for metabolism, physiological parameters or tissue clearance and see if particular combinations of parameters give rise to predictions of unusually large tissue doses. The distributions entered into the models could include physiological and metabolic profiles for children or for the elderly. Often the limiting factor in applying these models with distributions of parameters to estimate tissue dose/responses is our limited knowledge of parameter values in the general population or in specific groups in the general population.

DISCUSSION

Do Human Data Produce More Accurate Estimates of Risk?

This paper focuses on the dose–response assessment differences between humans and experimental animals. At first examination, a significant number of RfDs or RfCs, that we calculate from experimental animal data and where we use a 10-fold uncertainty factor for experimental animal to human extrapolation, are higher than EPA's human based values. This observation leads us to question whether the 10-fold factor is sufficient to protect human health for those animal-based RfDs and RfCs for which we lack human data to corroborate the nature or dose–response pattern of the critical effect. The data in Tables 1 and 2 and shown in Fig. 1 can be used to address this question, in part. In doing so, however, we suggest a more rigorous evaluation of the animal-based RfDs and RfCs that we calculate. This is because our estimations of RfDs or RfCs from experimental animal data have not undergone the same rigor in development and review as those made with the human data on IRIS (EPA, 2000b).

However, our analysis also show that a significant number of RfDs or RfCs, that we calculate from experimental animal data and where we use a 10-fold uncertainty factor for experimental animal to human extrapolation, are lower than the human based values. This observation leads us to question whether, for those animal-based RfDs and RfCs for which we lack human data to corroborate the nature or dose–response pattern of the critical effect, how many of these RfDs and RfCs err in a direction that overly protects human health? Unfortunately, because our work did not include in-depth and direct comparison of any dose–response curves of the critical effect between humans and experimental animals because of the general unavailability of such data, answers to such questions await additional analysis.

Although our analysis indicates that animal data can lead to either a higher or a lower risk value than human data, human data often have provided information that reduces uncertainty or identifies a completely different end point. For example, it is generally recognized that in developing RfDs or RfCs from animal data, the availability of adequate human data reduces or even obviates the need of uncertainty factors for extrapolating from animals to humans. This is based on the presumption that such adequate human data are more accurate predictors of human toxicity than animal data. In addition, EPA (2000b) notes several times when animal data are deemed inappropriate (e.g., warfarin, manganese, see Table 4), or the effect is different in at least some

TABLE 4
Description of Reasons Why an Animal-Based RfD or RfC Is Not Possible or Appropriate (Data from Tables 1 and 2)

Chemical name (as on EPA's IRIS)	Species/Type of study	Critical effect(s)
Beryllium RfC	Human occupational and community exposure Animal data	Beryllium sensitization and progression to chronic beryllium disease (CBD) No laboratory animal model fully mimics all features of human CBD
Cadmium RfD	Human chronic exposures from a variety of studies Animal data	Significant proteinuria Insufficient information exists in the IRIS file to make any determination of an RfD
Chromium (acid mists and aerosols) RfC	Human subchronic occupational Animal data	Nasal septum atrophy Experimental animal studies have not reported on nasal mucosal effects following inhalation exposures
Fluorine (soluble fluoride) RfD	Human epidemiology Animal data	Objectionable dental fluorosis Insufficient information exists in the IRIS file to make any determination of RfD
Hydrogen cyanide RfC	Human occupational Animal data	CNS symptoms and thyroid effects Insufficient information exists in the IRIS file to make any determination of RfC
Manganese RfC	Human occupation exposure Animal data	Impairment of neurobehavioral function IRIS states that animal toxicity data quantitatively support the human studies used as a basis of the RfC; quantified comparisons were not provided
Manganese RfD	Human data of several types Animal data	No LOAEL given. CNS effects appear to occur at higher doses IRIS states that human data are superior to any data obtained from animal toxicity studies as the basis of an RfD, since the physiologic requirements for manganese vary among species
1,1,2-Trichloro-1,2,2-trifluoroethane RfD	Human occupational exposure Animal data	Psychomotor impairment Insufficient information exists in the IRIS file to make any determination of RfD
Warfarin RfD	Human experimental Inappropriate	Increased prothrombin time IRIS states "Because of marked differences in the susceptibility of different species to the effects of warfarin, it would be inappropriate to derive an RfD from studies on lower animals"
Zinc and compounds RfD	Human experimental diet supplement Animal data	Decrease in erythrocyte superoxide dismutase concentration in adults Insufficient information exists in the IRIS file to make any determination of RfD

important aspect (e.g., arsenic, barium, beryllium and silver, see Tables 1 and 2). It is for these reasons, in part, that EPA gives higher priority to human studies (Barnes and Dourson, 1988; Dourson, 1994; EPA, 1994; Jarabek, 1994, 1995). Other organizations have the same preference in developing their hazard identification and dose–response assessments (Meek *et al.*, 1994; IPCS, 1994).

A recent text by Olson *et al.* (2000) also focuses on the hazard identification comparisons of experimental animals and humans for a series of 150 pharmaceutical compounds. These authors conclude that concordance between human and experimental animal toxicity was highest in the hematological, gastrointestinal, and cardiovascular areas and poorest for cutaneous, endocrine, and hepatobiliary and liver function abnormalities. Overall for 30% of the human toxicities, there was no relationship with toxicities seen in animals. This work supports the idea that in a significant number of times, human data would be essential for hazard identification and presumably for dose–response assessment.

Every cancer that has been first associated with a chemical in human studies, for which numerous examples exist (e.g., benzene, asbestos, chromium), supports the idea that human data result in a lower "safe" dose when compared to animal data. Animal bioassays may now be able to better predict carcinogenicity in humans than in the days prior to mandatory testing and the development of test guidelines, but other uncertainties are more likely to exist. The epidemiological data on dioxin suggest that humans are far less sensitive than animals (Hays *et al.*, 1997). In contrast, Crump *et al.* (1989) show rough similarities among human or animal studies for 23 chemicals for which adequate data were available to estimate lifetime cancer doses associated with a 25% incidence of tumor response (i.e., TD_{25}s) on the basis of mg/kg body weight dose. However, there is no reason to believe that for some other chemical the error in an assessment based on animal data would be the other way, with humans being far more sensitive (for example, see the results in Table 1 for 2,4-dinitrophenol). The question for either the cancer or noncancer end point is the same: if we ignore opportunities for collecting

human data to check our assessments, will we be basing standards on the wrong critical effect, or the wrong assumptions and consequently setting limits too high to be protective of the public's health?

A recommendation that might follow from these observations is that an evaluation of data from humans, when available and judged to be sufficient, is essential to the development of RfDs and RfCs. Such data seem preferable to using a uncertainty factor of 10 for experimental animal to human extrapolation, and often identify effects not seen in animal studies.

What Are Some of the Limitations of Our RfD/RfC Analysis?

The ratios of human to animal based RfDs and RfCs found in Tables 1 and 2 and in Fig. 1 should only be considered as a first approximation of the value of human data in the determination of a RfD or RfC for protection of the public's health. This is because the estimation of the RfD or RfC based on the human study found on EPA's IRIS (or elsewhere) was from:

- A thorough analysis of the available data based on a review of original studies,
- The development of a risk assessment document, and
- Debate in one or more internal ATSDR, EPA, or Health Canada peer review meetings, and, in at least the case of EPA, unanimous acceptance.

By contrast, the animal-based RfDs and RfCs that we develop here were generally based on summary information primarily found on EPA's IRIS or *TERA*'s *ITER*. These animal-based RfDs and RfCs generally did not have the benefit of the development of a risk document, nor extensive peer review. A more comprehensive analysis of animal-based RfDs and RfCs would have meant a comparable level of analysis and peer review, but clearly a much more intensive involvement, than this paper allows.

We have made these comparisons between human and animal data on the basis of the RfD or RfC. In other words, the comparisons were made after uncertainty factors have been applied to the NOAEL, LOAEL, BMD, or BMC. This approach is consistent with our goal, which is to evaluate how well human data, used with contemporary risk assessment practices, protect human health. The range of uncertainty factors that is used with the NOAELs, LOAELs, BMD, or BMC in these tables reflects the variety of data types and databases for different chemicals. Therefore, we based our comparison on the RfDs and RfCs themselves, not on the NOAELs, etc. However, we acknowledge that it would be perhaps better if comparisons could be made on specific matching end points between the experimental animal species and humans, such as what has recently been done by EPA for the reassessment of dioxin (http://www.epa.gov/ncea/pdfs/dioxin/dioxreass.htm).

If high-quality animal data are available, the default uncertainty factor is likely to be 100 for RfDs (e.g., nitrite, malathion) and a 10-fold difference between animal and average human NOAEL may be expected. For the chemicals with human and animal RfDs based on the same biological end point and data type (e.g., NOAELs), a ratio close to 1 corroborates the selection of an interspecies uncertainty factor of 10-fold. For example, for aldicarb (i.e., plasma cholinesterase inhibition) and baygon, the ratios are similar only with an uncertainty factor of 10-fold. A body of ongoing research seeks to evaluate and improve the basis for the uncertainty factors (e.g., Dourson *et al.*, 1996; Renwick and Lazarus, 1998; Meek *et al.*, 2000).

This issue of power of a study to detect change is also important, but generalizations about the power of different studies, such as the idea than animal studies are always more powerful than human studies because they often have more subjects, are difficult. We suggest a case by case comparison—a large case control study may have a few hundred people; a cohort study may have thousands, some cohorts follow up the people until nearly all have died, but some epidemiology studies have only limited exposure data.

A major issue here is the power of any study, but in particular, the power of a "negative" epidemiology study. In cancer risk assessment negative epidemiology studies have been used to set upper limits on the possible risk—if a study had the power to detect a 3-fold increase and does not, it assures us that risks above 3X are unlikely. Issues of power include not only study size, but also design and exposure assessment.

We defined several criteria for comparing the existing human-based RfDs and RfCs with the animal-based RfDs and RfCs we estimate in our paper. The lowest criterion was the comparison of RfDs and RfCs based on NOAELs for unrelated effects. This is, of course, the least preferred comparison because the human and animal data tell us different things about the toxicity of the chemical in question. We made this choice quite often in Tables 1 and 2.

The choice between a NOAEL or BMD (or their corresponding inhalation counterparts) for the same or related critical effect were the next best criteria in the comparison of human and animal-based RfDs and RfCs. Of course, these are more preferred comparisons because the human and animal data tell us more similar things about the toxicity of the chemical in question. We also made this choice quite often in Tables 1 and 2.

Some might suggest that such comparisons should be made on the basis of the BMD rather than the NOAEL. We have no inherent problem with this suggestion (our choices here were based on availability of BMDs). However, in general, the choice of either a NOAEL or BMD as the basis of this comparison correctly depends on the available data. For example, dog studies seldom have a sufficient number of animals to do an adequate BMD.

fferent types of effects with
underestimated. NOAELs
uperior to a BMD from ro-
s the critical effect, for ex-
effects model well. Numer-
l effects that are masked at
greater severity. The BMD
nodel these critical effects
depend on the NOAEL or
assessors often analyze the
at every dose of a chemical,
s in evaluating the results
similar chemicals, before
tical effect. Such judgement
estimation of BMDs, nor

t have sufficient data in or-
ponse curves of the critical
experimental animal-based
uch curves is recognized as
ion, but because many data
son, it is also the least likely

Clinical Designs Exist
inetics?

ting is to establish exposure
of human health in a va-
mental exposures, occupa-
sures to by-products of our
ctual tools for all these ex-
ercises require interpreta-
effects in animals or in ex-
minimally toxic levels and
insure that all members of
ve adequate protection. The
vary for criteria pollutants,
cupational toxicants. How-
rations of similar factors be-
okinetic models or tools are
itions where similar doses to
for different species or expo-
ct the numerator in the RfD
aling evaluates critical deter-
kinetics and aids in assessing
and identifying at-risk popu-
ons affect the denominator in
tion. These PK tools together
inetic data from volunteer
axistic studies with human
l data set from which sound
or protection of exposed indi-

)AEL need to be somewhat compara-
than the risk assessors' job of critical
ngly difficult with data sets having

PBPK approaches are important because they use scientific methods to as accurately as possible estimate and understand potential risk to humans and provide greater scientific certainty in risk characterization. The alternatives to PBPK are default assumptions, which have greater uncertainty.

If Human Data Are the Preferred Basis to Protect Human Health, Then What Does One Conclude if Human Data Lead to a Higher Risk Value Than One Based on Animal Data?

All ratios in Tables 1 and 2 that have a value greater than 1 demonstrate that the human based RfD or RfC is greater than the animal-based value. Ratios about equal to 10 would be expected if animals and humans were shown to be about equally sensitive, that is if NOAELs or LOAELs were similar (e.g., see chlorpyrifos or ethephon in Table 1). This is because the use of a 10-fold interspecies uncertainty factor with the animal NOAEL or LOAEL would result in a RfD or RfC that was about 10 times lower than a human-based RfD (and thus the ratio of human to animal-based risk value would be greater than 1). Even if the NOAEL in humans were lower than in animals, but by a factor of ~10 or less, the use of an interspecies uncertainty factor of 10-fold could result in a lower RfD or RfC based on animal data than the RfD or RfC based on human data.

Such a situation would also occur if the human data were suggesting a critical effect that the animal data were not. Table 1 shows several examples of this (e.g., nitrate, nitrite and selenium and compounds). In some cases, EPA and others judge that the animal data are not a reliable basis of the RfD or RfC and a ready comparison is not available or recommended (e.g., manganese, warfarin). This is an example of the important role of data other than whole animal bioassays, such as pharmacokinetics and pharmacodynamics, in the overall determination of RfDs and RfCs.

What is more problematic, and potentially much more serious, is when the human data suggest a lower RfD or RfC than the animal data, either because of greater sensitivity to the critical effect, or different critical effect. This occurs in 36% (12 of 33 comparisons) of the comparisons we performed, if no precision issues are considered, and occurs in 15% (5 of 33 comparisons) if precision is considered to be "perhaps an order of magnitude." In either case, the use of animal-based RfDs and RfCs, rather than those based on human data might be considered inappropriate because the public's health does not appear to be protected.

If we accept the premise that human data are more reliable and relevant for a human risk assessment, then it follows that human data should be used without bias as to whether their use results in a higher or lower RfD or RfC. Replacement of animal data with human data should be dependent on the quality of the human data

ıparable to the animal data it
ld be placed on a comparison
man data to the animal data
ıcertainty for human health of

D FUTURE DIRECTIONS

l a series of questions regarding
or risk assessment.

. human studies the best way to
lth risk from chemicals in our

given best by the many health
ıress this question. For exam-
leak *et al.*, 1994), IPCS (1994),
Dourson, 1988; EPA, 1994) each
n data rather than animal data
isk values. Based on our analy-
xamples, the use of human data
ion of RfDs and RfCs on EPA's
er than animal-based RfDs and
in this paper. Especially in these
uman-based RfDs and RfCs may
the public's health.
th agencies strive to resolve the
dentify criteria to foster the con-
that might lead to better protec-
lth?

ver to this question is a resound-
although limited, suggests a high
sons where the exclusive use of
ıd to RfDs and RfCs that do not
ılth. Moreover, in many cases the
ıgnized as having greater limita-
; human data, as reflected in gen-
ıty factors than those used with
ata.
ally should be asking is how good
animal data for protecting human
etermine when it would be better
ıan data rather than conducting
ıl study?
ignore available human data that
: or higher risk value?

ıere is no. Protecting the public's
) this work. However, it seems rea-
and regulatory agencies to further
uman data in the development of
RfDs and RfCs. Perhaps new cri-
ed so that such data can be used
se.

Additional analysis of the results we present here could be done. For example, we were able to use the complete listing of RfDs and RfCs based on human data from EPA's IRIS. Other organizations also have similar risk values based on human data, and these values might also be compared with those based on experimental animal data. In addition, further research might explore whether commonalities exist among target tissue or mode of action for those chemicals for which animal- and human-based RfDs and RfCs differ quantitatively. None of the animal-based RfCs that we estimated was below the human-based one found on IRIS, within the limits of precision being assumed. Was this deficiency due to a small sample size or was it related to the use of dosimetry for RfCs, but not yet for RfDs? Similarly, what are the implications for the health protectiveness of the vast majority of the RfDs and RfCs based on animal data, without any human data to act as a check?

We look toward future collaborations with other interested scientists for resolution of these and other issues.

ACKNOWLEDGMENTS

We thank Lynne Haber of Toxicology Excellence for Risk Assessment, Ruthann Rudel of Silent Spring Institute, Russ Savage of the National Institute for Occupational Safety and Health, and Bern Schwetz of the Food and Drug Administration for insightful comments. We also thank Meg Poehlmann for editing and administrative assistance. Support for this research was provided through the use of developmental reserve funds of Toxicology Excellence for Risk Assessment (TERA), Cincinnati, Ohio, a 501(c) (3) nonprofit organization.

REFERENCES

Andersen, M. E., and Jarabek, A. M. (2000). Nasal tissue dosimetry—Issues and approaches for "Category I" gases: A report on a meeting held in Research Triangle Park, NC, February 11–12, 1998. *Inhal. Toxicol.*, in press.

Andersen, M. E., Sarangapani, R., Frederick, C. B., and Kimbell, J. S. (1999). Dosimetric adjustment factors for methylmethacrylate derived from a steady-state analysis of a physiologically based clearance-extraction model. *Inhal. Toxicol.* 11, 899–928.

Andersen, M. E., Clewell, H. J., III, Gargas, M. L., MacNaughton, M. G., Reitz, R. H., Nolan, R., and McKenna, M. (1991). Physiologically based pharmacokinetic modeling with dichloromethane, its metabolite, carbon monoxide, and blood carboxyhemoglobin in rats and humans. *Toxicol. Appl. Pharmacol.* 108, 14–27.

Andersen, M. E., Clewell, H. J., III, Gargas, M. L., Smith, F. A., and Reitz, R. H. (1987). Physiologically-based pharmacokinetics and the risk assessment process for methylene chloride. *Toxicol. Appl. Pharmacol.* 87, 185–205.

Barnes, D. G., and Dourson, M. L. (1988). Reference dose (RfD): Description and use in health risk assessments. *Regul. Toxicol. Pharmacol.* 8, 471–486.

Barton, H. A., Andersen, M. E., and Clewell, H. J., III (1998). Harmonization: Developing consistent guidelines for applying mode of

...son to cancer and noncancer risk as-
...sess. 4, 75–115.
...ing biological information in quanti-
...ample with methylene chloride. Tox-

...pp, A. (1989). Choice of dose mea-
...genic risk from animals to humans:
... 23 chemicals. Health Phys. 57, 387–

... of the USEPA Joint Science Advi-
Panel, Data from Testing on Human
...mber 30, 1998.
... for establishing oral reference doses
... Essential Elements. (W. Mertz, C. O.
...), pp. 51–61. ILSI Press, Washington,

...and Robinson, D. (1996). Evolution of
...ctors in noncancer risk assessment.
...4, 108–120.
...k, B., Renwick, A., Ohanian, E., and
...rable intake: Re-evaluation of toxicoki-
...rtainty factors. Biol. Trace Elem. Res.

Appraisal of Epidemiological Studies
Univ. Press, Oxford.
...n Agency) (1994). Methods for Deriva-
Concentrations and Application of In-
...0/8-90-066F, October. Office of Health
...ment, Washington, DC.
...on Agency) (1999). The Office Of Pes-
Determination of the Appropriate FQPA
...Tolerance-Setting Process. May. Office

...on Agency) (2000a). Science Advisory
...ee Review Draft Report of the Joint
... Data from Testing of Human Subjects.
...a.gov/sab/Reports/2000report/2000dra-
...ft.
...on Agency) (2000b). Integrated Risk In-
National Center for Environmental As-
...individual chemicals and the glossary
Available online at http://www.epa.gov/

... L. (1998). The inexact science of risk
...ns for risk management). Human Ecol.

...bramaniam, R. P., Black, K. A., Finch,
..., K. T., Morris, J. B., and Ultman, J. S.
...brid computational fluid dynamics and
...lation model for interspecies dosimetry
...ors in the upper airways. Toxicol. Appl.

...stration) (1997). FDA Public Health Ad-
Heart Disease in Patients Receiving Con-
...d Phentermine. July.
W., Clewell, H. J., III, Andersen, M. E.,
A physiologically based model for in vivo
...terase by diisopropyl fluorophosphate.
...186, 296–310.
... K. (1983). Physiologically based phar-
...nciples and applications. J. Pharm. Sci.

...h, N., and Paustenbach, D. (1997). The
...nimals and humans to the carcinogenic

hazard posed by exposure to 2,3,7,8-TCDD: An analysis using standard and internal measures of dose. Chemosphere 34(5–7), 1507–1522.

ILSI (International Life Sciences Institute) (1997). An evaluation of EPA's proposed guidelines for carcinogen risk assessment using chloroform and dichloroacetate as case studies: Report of an expert panel. November. Washington, D.C.

IPCS (International Programme on Chemical Safety) (1994). Derivation of guidance values for health-based exposure limits. Environmental Health Criteria No. 170: Assessing Human Health Risks of Chemicals. World Health Organization, Geneva.

Jarabek, A. M. (1994). Inhalation RfC methodology: Dosimetric adjustments and dose-response estimation of noncancer toxicity in the upper respiratory tract. Inhal. Toxicol. 6(Suppl.), 301–325.

Jarabek, A. M. (1995). The application of dosimetry models to identify key processes and parameters for default dose-response assessment approaches. Toxicol. Lett. 79, 171–184.

Lee, ET. (1980). Statistical Methods for Survival Data Analysis. Lifetime Learning Publications, CA.

MacGregor, J. T., Collins, J. M., Sugiyama, Y., Tyson, C. A., Dean, J., Smith, L., Andersen, M., Curren, R., Houston, J. B., Kadlubar, F. K., Kedderis, G. L., Krishnan, K., Li, A., Parchment, R. E., Thummel, K., Tomaszewski, J. E., Ulrich, R., Vickers, A. E. M., and Wrighton, S. A. (2000). In vitro Human tissue models in risk assessment: Report of a consensus-building workshop in vitro human tissue models in risk assessment. Toxicol. Sci., in press.

Meek, M. E., Newhook, R., Liteplo, R. G., and V. C. Armstrong. (1994). Approach to assessment of risk to human health for priority substances under the Canadian Environmental Protection Act. Environ. Carcinogen. Ecotoxicol. Rev. C12(2), 105–134.

Meek, B., Renwick, A., Ohanian, E., Dourson, M., Lake, B., Naumann, B., and Vu, V. (2001). Guidelines for application of compound specific adjustment factors (CSAF) in dose/concentration response assessment. In press.

Murray, F. J., and Andersen, M. E. (2000). Data-derived uncertainty factors: Boric acid (BA) as a case study. Hum. Ecol. Risk Assess., in press.

NAS (National Academy of Sciences) (1983). Risk Assessment in the Federal Government: Managing the Process. National Academy Press, Washington, DC.

NAS (National Academy of Sciences) (1994). Science and Judgment in Risk Assessment. National Academy Press, Washington, DC.

NCEA (National Center for Environmental Assessment) (2000). Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and Related Compounds. Online at http://www.epa.gov/ncea/pdfs/dioxin/dioxreass.htm.

NRC (National Research Council) (1986). Dose-Route Extrapolations: Using Inhalation Toxicity Data to Set Drinking Water Limits. Chapter 6, Drinking Water and Health. Volume 6: National Academy Press, Washington, DC.

Okada, R., Leininger, J., and Froines, J. (1999). Subchronic toxicity study of sodium arsenite in methyl-deficient male C57BL/6 mice. In: Arsenic Exposure and Health Effects (W. Chappell, C. Abernathy, and R. Calderon, Eds.), pp. 225–232. Elsevier, Amsterdam, The Netherlands.

Olson, H., Betton, G., Robinson, D., et al. (2000). Concordance of the toxicity of pharmaceuticals in humans and in animals. Regul. Toxicol. Pharmacol. 32, 56–67.

Plowchalk, D. R., Andersen, M. E., and Bogdanffy, M. S. (1997). Physiologically-based modeling of vinyl acetate uptake, metabolism and intracellular pH changes in the rat nasal cavity. Toxicol. Appl. Pharmacol. 142, 386–400.

BEST COPY AVAILABLE

...son to cancer and noncancer risk as-
...sess. 4, 75–115.

...ing biological information in quanti-
...xample with methylene chloride. Tox-

...pp, A. (1989). Choice of dose mea-
...sponse risk from animals to humans:
...23 chemicals. Health Phys. 57, 337–

...t of the USEPA Joint Science Advi-
...Panel, Data from Testing on Human
...ember 30, 1998.

...s for establishing oral reference doses
...f Essential Elements. (W. Mertz, C. O.
...s.), pp. 51–61. ILSI Press, Washington,

...and Robinson, D. (1996). Evaluation of
...actors in noncancer risk assessment.
...4, 108–120.

...ak, H., Renwick, A., Ohanian, E., and
...able intake: Re-evaluation of toxicoki-
...rtainty factors. Biol. Trace Elem. Res.

Appraisal of Epidemiological Studies
...Univ. Press, Oxford.

...n Agency) (1994). Methods for Deriva-
Concentrations and Application of In-
...0/6-90-066F, October. Office of Health
...ment, Washington, DC.

...n Agency) (1999). The Office Of Pes-
...Determination of the Appropriate FQPA
...n Tolerance-Setting Process. May. Office

...ion Agency) (2000a). Science Advisory
...ee Review Draft Report of the Joint
...n Data from Testing of Human Subjects.
...a.gov/sab/Reports/2000report/2000dra-
...ft.

...n Agency) (2000b). Integrated Risk In-
...National Center for Environmental As-
...individual chemicals and the glossary
...Available online at http://www.epa.gov/

...L. (1998). The inexact science of risk
...es for risk management. Human Ecol.

...ubramaniam, R. P., Black, K. A., Finch,
..., K. T., Morris, J. B., and Ultman, J. S.
...ybrid computational fluid dynamics and
...lation model for interspecies dosimetry
...ors in the upper airways. Toxicol. Appl.

...stration) (1997). FDA Public Health Ad-
...Heart Disease in Patients Receiving Con-
...d Phentermine. July.

...W., Clewell, H. J., III, Andersen, M. E.,
...A physiologically based model for in vivo
...terase by diisopropyl fluorophosphate.
...186, 296–310.

...R. K. (1983). Physiologically based phar-
...nciples and applications. J. Pharm. Sci.

...h, N., and Paustenbach, D. (1997). The
...nimals and humans to the carcinogenic

hazard posed by exposure to 2,3,7,8-TCDD: An analysis using standard and internal measures of dose. Chemosphere 34(5–7), 1507–1522.

ILSI (International Life Sciences Institute) (1997). An evaluation of EPA's proposed guidelines for carcinogen risk assessment using chloroform and dichloroacetate as case studies: Report of an expert panel. November. Washington, D.C.

IPCS (International Programme on Chemical Safety) (1994). Derivation of guidance values for health-based exposure limits. Environmental Health Criteria No. 170: Assessing Human Health Risks of Chemicals. World Health Organization, Geneva.

Jarabek, A. M. (1994). Inhalation RfC methodology: Dosimetric adjustments and dose-response estimation of noncancer toxicity in the upper respiratory tract. Inhal. Toxicol. 6(Suppl.), 301–325.

Jarabek, A. M. (1995). The application of dosimetry models to identify key processes and parameters for default dose–response assessment approaches. Toxicol. Lett. 79, 171–184.

Lee, ET. (1980). Statistical Methods for Survival Data Analysis. Lifetime Learning Publications, CA.

MacGregor, J. T., Collins, J. M., Sugiyama, Y., Tyson, C. A., Dean, J., Smith, L., Andersen, M., Curren, R., Houston, J. B., Kadlubar, F. K., Kedderis, G. L., Krishnan, K., Li, A., Parchment, R. E., Thummel, K., Tomaszewski, J. E., Ulrich, R., Vickers, A. E. M., and Wrighton, S. A. (2000). In vitro Human tissue models in risk assessment: Report of a consensus-building workshop in vitro human tissue models in risk assessment. Toxicol. Sci., in press.

Meek, M. E., Newhook, R., Liteplo, R. G., and V. C. Armstrong. (1994). Approach to assessment of risk to human health for priority substances under the Canadian Environmental Protection Act. Environ. Carcinogen. Ecotoxicol. Rev. C12(2), 105–134.

Meek, E., Renwick, A., Ohanian, E., Dourson, M., Lake, B., Naumann, B., and Vu, V. (2001). Guidelines for application of compound specific adjustment factors (CSAF) in dose/concentration response assessment. In press.

Murray, F. J., and Andersen, M. E. (2000). Data-derived uncertainty factors: Boric acid (BA) as a case study. Hum. Ecol. Risk Assess., in press.

NAS (National Academy of Sciences) (1983). Risk Assessment in the Federal Government: Managing the Process. National Academy Press, Washington, DC.

NAS (National Academy of Sciences) (1994). Science and Judgment in Risk Assessment. National Academy Press, Washington, DC.

NCEA (National Center for Environmental Assessment) (2000). Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and Related Compounds. Online at http://www.epa.gov/ncea/pdfs/dioxin/dioxreass.htm.

NRC (National Research Council) (1986). Dose-Route Extrapolations: Using Inhalation Toxicity Data to Set Drinking Water Limits. Chapter 6. Drinking Water and Health, Volume 6: National Academy Press, Washington, DC.

Ohaji, R., Leininger, J., and Frelman, J. (1998). Subchronic toxicity study of sodium arsenite in methyl-deficient male C57BL/6 mice. In: Arsenic Exposure and Health Effects (W. Chappell, C. Abernathy, and R. Calderon, Eds.), pp. 225–232. Elsevier, Amsterdam, The Netherlands.

Olson, H., Betton, G., Robinson, D., et al. (2000). Concordance of the toxicity of pharmaceuticals in humans and in animals. Regul. Toxicol. Pharmacol. 32, 56–67.

Plowchalk, D. R., Andersen, M. E., and Bogdanffy, M. S. (1997). Physiologically-based modeling of vinyl acetate uptake, metabolism and intracellular pH changes in the rat nasal cavity. Toxicol. Appl. Pharmacol. 142, 386–400.

BEST COPY AVAILABLE

Reitz, R. H., Mendrala, A. L., and Guengerich, F. P. (1989). *In vitro* metabolism of methylene chloride in human and animal tissues: Use in physiologically based pharmacokinetic models. *Toxicol. Appl. Pharmacol.* 97, 230–246.

Renwick, A. G. (1993). Data derived safety factors for the evaluation of food additives and environmental contaminants. *Food Addit. Contam.* 10(3), 275–305.

Renwick, A., and Lazarus, N. R. (1998). Human variability and non-cancer risk assessment–An analysis of the default uncertainty factor. *Regul. Toxicol. Pharmacol.* 27, 3–20.

Reuss, E. (2000). Monitoring human subjects and clinical trials. *Scientist* May 15, p. 6.

SOT (Society of Toxicology) (2000). *The Value and Ethics of Using Human Data for the Registration of Pesticides.* 39th Annual Meeting, March 23.

TERA (Toxicology Excellence for Risk Assessment) (2000). *International Toxicity Estimates for Risk (ITER) Database.* Online at www.tera.org.

Thomas, R. S., Bigelow, P. L., Keefe, T. J., and Yang, R. S. H. (1998). Variability in biological exposure indices using physiologically based pharmacokinetic modeling and Monte Carlo simulation. *Amer. Ind. Hyg. Assoc. J.* 57, 23–32.

Vesini, M. D., and Ovesini, F. (2000). *Evaluation of Renal Clearance of Boric Acid in Non-pregnant and Pregnant Sprague–Dawley Rats.* Final Report. Univ. California, Irvine, April.

Center for Regulatory Effectiveness

Suite 700
11 Dupont Circle, N.W.
Washington, D.C. 20036
Tel: (202) 265-2383 Fax: (202) 939-6969
www.TheCRE.com

August 22, 2000

Ms. Carol M. Browner
Administrator
Environmental Protection Agency
1200 Pennsylvania Ave., N.W.
Washington, DC 20460

Dear Administrator Browner:

We have conducted a comprehensive survey within EPA regarding the Agency's use of clinical human test data. We are furnishing you the results of our research and seek your views on its results.

EPA's Office of Pesticides Programs recently banned the use of any clinical human test data during its regulation of pesticides and herbicides under the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA") and the Food Quality Protection Act ("FQPA"). In light of this new ban, and given the results of CRE's survey, we request that EPA respond to the following questions:

(1) Does EPA agree with CRE that the Pesticides Office's new ban on clinical human test data differs from and is inconsistent with the Pesticides Office's own prior practice and procedure?

(2) Does EPA agree with CRE that the Pesticides Office's new ban on clinical human test data differs from and is inconsistent with the current practice and procedure of other EPA Offices and Programs?

-- For example, CRE understands that other EPA Offices and Programs are bathing human test subjects in water contaminated with toxic substances.

-- As another example, CRE understands that other EPA Offices and Programs currently operate "Human Exposure Chambers" where human test subjects are exposed to toxic substances.

CRE also requests that EPA immediately reverse the Pesticides Office's refusal to consider any clinical human test data, and immediately allow consideration of such data, so long as it is generated in accordance with either the Common Rule or the Declaration of Helsinki. If the Pesticides Office wants to reconsider the use of clinical human test data, then EPA must address this issue in a public-notice-and-comment rulemaking conducted in accordance with the rulemaking requirements of the Administrative Procedure Act ("APA"). In the interim, clinical human test data must be accepted and utilized by the agency. Given EPA's own generation and use of clinical human test data in many other contexts, CRE doubts that there would be any rational basis for a rule banning such data during the regulation of pesticides and herbicides.

This letter is based on CRE's extensive review of EPA documents and discussions with EPA personnel. CRE's findings and conclusions are set forth below.

CRE'S SURVEY OF HUMAN TESTING PRACTICES AND PROCEDURES AT EPA

EPA's Pesticides Office Recently Banned Use of Clinical Human Test Data.

On July 27, 1998, EPA announced that the Pesticides Office would no longer consider any human test data when regulating pesticides or herbicides under FIFRA and the FQPA. EPA Statement dated July 27, 1998. In a Staff Background Paper prepared for the November 30, 1999 meeting of SAB/SAP Joint Subcommittee on Data from Human Subjects, EPA stated that "[t]he Agency's policy continues as it was first articulated in July 1998: we will not rely on [human] studies to support final decisions under the Food Quality Protection Act" until a final policy is in place regarding use of these studies. EPA spokespersons were recently quoted as stating, "We see no reason to change our policy, and our policy will remain no human testing of pesticides or toxics." BNA Daily Environment Report, June 8, 2000, p. A-11; *Washington Post*, June 7, 2000, p. A-02. Since its July 27, 1998 statement on this issue, the Pesticides Office has in several cases refused to consider clinical human tests when making FIFRA and FQPA regulatory decisions. Since that time, the Pesticides Office has not considered clinical human test data when making FIFRA and FQPA regulatory decisions.

Before 1998, the Pesticides Office Considered Clinical Human Test Data.

Until 1998, the Pesticides Office actively accepted and evaluated data from privately funded studies of human volunteers when regulating pesticides and herbicides. See EPA "Staff Background Paper" submitted to SAB/SAP Subcommittee on Data from Human Subjects for its November 30, 1999 Meeting. In fact, EPA has often stated that human test data are ethically acceptable and often scientifically preferable. For example, EPA's "Guidelines for Neurotoxicity Risk Assessment" dated May 14, 1998, at 35, explains that it is:

> ... ethically possible to perform human laboratory studies and obtain data relevant to the risk assessment process. Information from experimental human exposure studies have been used to set occupational exposure limits...[and] contributed to risk assessment and the setting of exposure limits for several solvents and other chemicals with acute reversible effects. Human exposure studies sometimes offer advantages over epidemiological field studies.

EPA's Neurotoxicity Guidelines are frequently used when performing risk assessments and making tolerance decisions for herbicides and pesticides. These Guidelines were published in final form in the *Federal Register* after public notice of and an opportunity to comment on proposed Guidelines. 63 FR 26926 (May 14, 1998); 60 FR 52032 (Oct. 14, 1995).

EPA Still Considers and Generates Human Test Data in Other Contexts.

At the December, 1998 meeting of the SAP/SAB Subcommittee on Data from Human Subjects, EPA representatives presented information on the Agency's acceptance and use of clinical human test data for the period from January 1, 1990 through August 31, 1998. During that period 26 human effects studies based on intentional clinical exposure were submitted that addressed metabolism, pharmokinetics, and absorption, and 8 that addressed a No Adverse Effects Level ("NOAEL").

EPA further noted in its "Staff Background Paper" prepared for the November, 1999 meeting of the SAB/SAP Subcommittee on Data from Human Subjects that the Agency itself still conducts and supports clinical tests involving human exposure to toxic substances, including the following:

- MTBE (methy tertiary butyl ether)
- Ozone
- SO2 (sulphur dioxide)
- NO2 (nitrogen dioxide)
- CO (carbon monoxide)

- Air particulate matter and acidic particles
- Methy mercury
- Hydrofluorocarbons

EPA's Office of Prevention, Pesticides, and Toxic Substances is in charge of the FIFRA and FQPA regulatory program. This EPA Office includes both the Office of Pollution Prevention and Toxics ("OPPT") and the Pesticides Office. OPPT, as well as EPA's Air Office and Water Office, continue to use human test data for several purposes, including risk assessments. *See, e.g.*, 65 FR 14186 (Mar. 15, 2000). Current practice by OPPT, the Air Office, and the Water Office is irreconcilable with Pesticides Office's new ban on clinical human test data.

EPA has its own "Human Studies Division" which still conducts clinical human studies involving toxic substances. Many of these EPA human tests are conducted at EPA's "Human Studies Facility" in Chapel Hill, North Carolina. EPA's "Human Studies Facility" contains eleven "Human Exposure Chambers" where human test subjects are exposed to hazardous air pollutants and other toxic substances.

EPA's Air Office is engaged in a major regulatory review of MTBE, a gasoline additive. In support of this effort, EPA's National Exposure Research Laboratory ("NERL") is conducting several human tests. These include, as described by NERL:

> "Human Exposure to Methyl Tertiary-Butyl Ether (MTBE) While Bathing with Contaminated Water";
>
> "Inhalation and Dermal Exposure to MTBE using Continuous Breath Analysis"; and
>
> "Controlled methyl tertiary-butyl ether (MTBE) exposure to humans through dermal, ingestion, and inhalation routes and the resultant biomarker tertiary butyl alcohol (TBA) as measured in exhaled breath and venous blood."

If CRE's research and survey are correct, then EPA itself is bathing human test subjects with contaminated water and making them breathe contaminated air. How can EPA reconcile its own human tests with the Pesticides Office's new ban on any industry-submitted clinical human test data?

THE PESTICIDES OFFICE'S NEW BAN ON CLINICAL HUMAN TEST DATA VIOLATES THE APA

The Pesticides Office's new ban on clinical human test data is a legislative rule under the Federal Administrative Procedure Act ("APA"), 5 U.S.C. §§ 551 et seq. Therefore, it is subject to the APA's rulemaking requirements.

The APA's definition of "rule" includes a statement of general or particular applicability and future effect designed to implement law or policy. 5 U.S.C. § 551(4). This definition is broadly construed to include not only formal regulations but other types of documents and even unwritten policies and procedures. *See, e.g., Ciba-Geigy v. EPA*, 801 F.2d 430 (D.C. Cir. 1986) (EPA's letter to the regulated community constitutes "legislative rule"); *United States v. Articles of Drug*, 634 F. Supp. 435 (N.D. Ill. 1985), *vacated as moot*, 818 F. 2d 569 (7th Cir. 1987) (unwritten procedures regarding the importation of animal drugs are rules under the APA).

EPA's new refusal to consider industry-submitted pesticide and herbicide human test data is not an "interpretive rule" under the APA. The "interpretive rule" exception to the APA's rulemaking requirements does not apply to rules and policies that have a "binding effect" on either EPA or private parties. *See McLouth Steel Products Corp.* v. *Thomas*, 838 F. 2d 1317, 1320 (D.C. Cir. 1988) ("If it appears that a so-called [interpretive rule] is in purpose or likely effect one that narrowly limits administrative discretion, it will be taken for what it is–a binding rule of subsequent law").

EPA cannot avoid the APA's rulemaking requirements by labeling the Pesticide Office's new refusal to consider human test data an "interim policy." "EPA's label of an agency action, although one factor to be considered, does not control whether the action is in fact a rulemaking. Instead, "it is the substance of what the [agency] has purported to do and has done which is decisive." *Limerick Ecology Action, Inc. v. United States Nuclear Regulatory Commission*, 869 F. 2d 719, 733 (3rd Cir. 1989) (quoting *Columbia Broadcasting System v. United States*, 316 U.S. 406, 407, 416 (1942)). *See also American Trucking Ass'n v. United States*, 688 F. 2d 1337, 1348 (11th Cir. 1982) ("the decision to reverse a longstanding and uniform practice by revoking all outstanding authorities of a particular type and implicitly indicating that no such authorities will be issued in the future is clearly a rule").

The Pesticide Office's new ban on clinical human test data establishes a binding norm that must be followed in all cases involving the regulation of pesticides and herbicides. Therefore, this new ban violates the APA because it was never proposed for public notice and comment in accordance with the APA's rulemaking provisions.

CONCLUSION

Based on CRE's research and survey, the Pesticides Office's new ban on human test data differs from and is inconsistent with the Office's past practice and procedure. It also differs from and is inconsistent with EPA's current practice and procedure in many other Offices and Programs. We request that you state whether you agree or disagree with CRE's conclusions. CRE further requests

that EPA initiate an APA rulemaking before the Pesticides Office continues its ban on the use of clinical human test data. Finally, CRE can see no rational basis for such a ban given EPA's current practice of generating and using clinical human test data in many other regulatory contexts.

We thank you for your prompt response to these requests.

Sincerely,

Jim J. Tozzi
Member, CRE Board of Advisors

EXAMPLES OF EPA USE OF CLINICAL HUMAN TEST DATA

There follow some detailed citations and quotations for examples of instances in which human volunteer test data played a significant or substantial role in setting of a regulatory standard by EPA. Some such examples include controlled human volunteer studies involving exposures to MTBE and particulates supported or conducted by EPA's Human Studies Division of its National Health and Environmental Effects Research Laboratory ("NHEERL").[1]

These examples are only from EPA programs. Other examples of support for human volunteer testing and use of such test data in standards-setting could be provided from other Federal agencies.

For several of the substances below, human volunteer test data which had previously been a principal factor in determining a consensus LOAEL and/or NOAEL and RfD (reference dose) for regulatory purposes, as recorded in the Agency's public IRIS database, was later explicitly excluded from a regulatory decision based on uncertainty over the position the Agency would take on acceptability of such data following its July 27, 1998 expression of concern over the use of such data. That situation, of course, remains unresolved.

Also, in the case of several of the pesticides, only the current RfD or a drinking water standard is available for purposes of preparing this document. While tolerances for residues have previously been set for such pesticides, the *Federal Register* tolerance notices do not provide any information on the scientific basis, and many of the underlying risk assessments are not available on the Internet and would have to be obtained through a freedom of information request. In the interests of expediency, therefore, we have not waited to obtain FOIA information for those pesticides and have assumed that, consistent with its usual approach prior to July 27, 1998, the Agency employed the consensus RfD in setting the crop tolerances. We believe this assumption is appropriate given that much of the debate over the use of human volunteer studies of pesticides has been in the context of determining LOAELs, LOELs, NOAELs, and NOELs, as well as simply the ethics of enrolling volunteers to allow themselves to be exposed to potentially toxic chemicals.

This document is not comprehensive in that it does not investigate regulatory standards for some other programs such as CERCLA and RCRA. Instead, it relies on recognition that EPA's IRIS RfDs are a primary determinant in setting all of the Agency's regulatory standards for non-cancer health risks.

---

[1] See, e.g., Prah JD, Goldstein GM, Devlin R, Ashley D, House D, Cohen KL, and Gerrity T. 1994. Sensory, symptomatic, inflammatory, and ocular responses to and the metabolism of methyl tertiary butyl ether in a controlled human exposure experiment. *Inhal Toxicol* 6:521-38; "Oxygenates in Water: Critical Information and Research Needs", EPA/600/R-98/048, Dec. 1998, p. 25.

The substance-specific information below on use of human volunteer test data in setting regulatory standards or RfDs is presented alphabetically.

1. Aldicarb, aldicarb sulfoxide, and aldicarb sulfone

Aldicarb is a carbamate insecticide. On July 1, 1991 (56 Fed.Reg. 30266), EPA set MCLGs and MCLs[2] for aldicarb and its metabolites. The MCLGs were based on the RfD as adjusted with standard uncertainty factors and exposure adjustments. The RfD of 0.0002 mg/kg/day and MCLG of 0.001 mg/l for aldicarb and aldicarb sulfoxide were derived from no-effect levels observed in an experimental animal study and a human volunteer study involving four healthy male volunteers (Haines, 1971). At 30269. Although aldicarb sulfone was considered to be less toxic, the same MCLG was set for it using a higher uncertainty factor because the MCLG was based solely on the NOAEL in an animal study and there were no human clinical data available as there were for aldicarb and aldicarb sulfoxide. The Agency indicated in the earlier rulemaking proposal that "[i]f human data with aldicarb sulfone become available to the Agency, the extra 3-fold [sic] used in the RfD calculation for aldicarb sulfone may not be necessary." 56 Fed.Reg. 3600, 3606 (Jan. 30, 1991).

In 1992, as reflected in EPA's online IRIS database, a new human volunteer study for acute human oral exposure to aldicarb was submitted to EPA. The study was a double-blind, placebo-controlled study involving 38 men and 6 women. (Cited in the IRIS entry as Rhone-Poulenc Ag Company. 1992. A Safety and Tolerability Study of Aldicarb at Various Dose Levels in Healthy Male and Female Volunteers. Inveresk Clinical Research Report No. 7786, MRID No. 423730-01. HED Doc. No. 0010459.) The IRIS database shows that the RfD for aldicarb was revised on 11/01/1993 to 0.001 using this new human volunteer study as the principal study, vs. the 0.0002 RfD used for the July 1, 1991 final drinking water MCLG, and using an uncertainty factor of 10, rather than the UF of 100 that was used for the MCLG.[3]

2. Barium and barium compounds

Barium and barium compounds are a metal and its soluble salts that are found in groundwater in many parts of the country due to various industrial processes. On July 1, 1991,

---

[2] MCLs (maximum contaminant levels) are set "as close as feasible" to the MCLGs (maximum contaminant level goals).

[3] On May 27, 1992, EPA "postponed" the drinking water standards for aldicarb and its metabolites, but kept monitoring requirements in place. 57 Fed.Reg. 110551 et seq. No further action has been taken by EPA on these drinking water standards.

EPA set a final drinking water MCLG for barium and barium compounds based on an RfD of 0.07 mg/kg/day derived from a human volunteer study in which barium chloride in drinking water was administered to 11 healthy male volunteers (cited in the IRIS database as "Wones, RG,; Stadler, BL; Frohman, LA. (1990) Lack of effect of drinking water barium on cardiovascular risk factor. Environ Health Perspect 85:355-59", and cited in the EPA final drinking water rule as "Wones 1990".) An uncertainty factor of 3 was applied to the NOAEL. 56 Fed.Reg. 30266, 30272.

The latest IRIS database entry for barium and barium compounds, last revised 1/21/99, continues to show an RfD of 0.07 using an uncertainty factor of 3. Unlike the 1991 drinking water final rule (above), however, it does not state that the RfD is based solely on the Wones et al. 1990 human volunteer study; rather, it states: "No single study is appropriate as the basis for a lifetime RfD for barium. The RfD is based on a weight-of-evidence approach that focuses on four co-principal studies: the Wones et al. (1990) experimental study in humans, the Brenniman and Levy (1984) epidemiologic study, and the subchronic and chronic rat studies that employed adequate diets and investigated both cardiovascular and renal endpoints (NTP, 1994)."

3. **Baygon (propoxur)**

Baygon is a carbamate insecticide. However, because it is not used on crops, no tolerance for residues have been set. EPA's online IRIS database shows that the RfD, last revised 07/01/1992, was based on a single human volunteer study in which an unspecified number of subjects received a single oral dose. A NOEL could not be determined, and the RfD was based on an LEL with an uncertainty factor of 100. The study is cited as "Vandekar, M., R. Plestina and K. Wilhelm. 1971. Toxicity of carbamates for mammals. Bull. World. Health. Org. 44:241-249."

4. **Carbon monoxide**

EPA set air quality standards (NAAQS) for carbon monoxide in 1971. In 1985, it completed a review of the standards and decided not to revise the 1971 standard and to revoke the secondary standard. In 1994, EPA completed another review of the NAAQS and determined that revisions were not appropriate. 59 Fed. Reg. 38906 et seq. (Aug. 1, 1994). The 1994 decision was based primarily on controlled human volunteer studies of patients suffering from angina pectoris, ischemic heart disease, and obstructive coronary artery disease. 59 Fed.Reg. at 38909-11. The data from those studies were supported by numerous controlled human volunteer studies of the effects of carbon monoxide on oxygen uptake and exercise performance in healthy individuals. 59 Fed.Reg. at 38909, 38911. The notice of the final decision also discussed the findings from numerous controlled human volunteer studies for neurobehavioral effects such as changes in visual perception, hearing, motor performance, sensorimotor performance, and vigilance, but concluded that because the cardiovascular studies showed effects at lower levels, they should remain the primary focus. 59 Fed.Reg. at 38911.

Air quality standards, and reviews of those standards, are based on "Criteria Documents", followed by "Staff Papers", and supplemented by CASAC evaluation of the those two documents. The most recent Criteria Document for carbon monoxide was published in June 2000. AIR QUALITY CRITERIA FOR CARBON MONOXIDE. USEPA EPA 600/P-99/001F. 01, June 2000. That CD states that the "[h]ealth assessment provided in this document supports and substantiates the conclusions drawn in the previous [criteria] document." (Abstract.) The previous criteria document was completed in 1991 and was one of the source documents for the review discussed above that was completed in 1994. The 2000 CD goes on to state: "Although the scientific data have changed little since 1991, controlled-exposure studies continue to provide the most quantitative evidence on low-level CO effects in humans. *Id.*, section 6.1 ("Health Effects of Exposure to Carbon Monoxide"), p. 6-1.

5. Chlorpyrifos

Chlorpyrifos is an organophosphate insecticide. EPA's online IRIS database shows that the oral RfD for chlorpyrifos was last revised in 1988. The RfD was set at 0.003 mg/kg/day, using a NOEL of 0.03 mg/kg/day and a LOEL of 0.10 mg/kg/day, and an uncertainty factor of 10. The NOEL and LOEL are based on a controlled human volunteer study of 16 males treated for 20 days at a low and mid-range doses, and for 9 days at a higher dose. This "principal study" for the RfD is cited as "Dow Chemical Company. 1972. Accession No. 112118." This RfD has presumably been the basis for tolerances assigned to the product.

On June 8, 2000, EPA published (and subsequently made available online) a revised Human Health Risk Assessment for chlorpyrifos. The revised assessment stated: "In light of the developing Agency policy on use of toxicology studies employing human subjects, HED [the Health Effects Division of EPA's Office of Pesticide Programs] selected doses and endpoints for risk assessment based solely on animal studies." At 2. The Agency derived from the animal data an acute NOAEL of 0.5 mg/kg/day and an acute LOAEL of 1.0. Although the animal study NOAEL and LOAEL were more than 10x higher than the human levels, because animal studies were used, the Agency applied an extra 10x inter-species uncertainty factor (UF) to calculate an acute dietary RfD of 0.005 mg/kg/day. This animal-based RfD was still higher than the previous 0.003 RfD based on human volunteer studies. However, the Agency's FQPA Safety Factor Committee of the HED decided that an additional 3x FQPA safety factor should be applied, resulting in a cumulative UF of 300 and reducing the RfD to 0.0017. Memorandum dated Oct. 14, 1999 from David Soderberg to Mark Hartman; Memorandum dated June 2, 1999 on "Replacement of Human Study Used in Risk Assessments" from Jess Rowland to Steve Knizner; Memorandum dated April 5, 1999 on "Report of the FQPA Safety Factor Committee" from Brenda Tarplee to Deborah Smegal. Subsequently, the Agency's Division Directors and senior scientists (DD-SS) overruled the FQPA Safety Factor Committee and "recommended that the FQPA safety factor should be **retained at 10X** for the protection of infants and children from exposure to chlorpyrifos." Revised Risk Assessment at 3, original emphasis. Retention of the

this FQPA 10x factor further reduced the acute RfD to 0.0005. in place of the previous RfD of 0.003.

6. Ethephon

Ethephon is an organic phosphorus compound used as a plant growth regulator due to its ethylene-releasing properties. It also has cholinesterase inhibiting effects. The online IRIS database RfD shows it was last revised on 03/01/1991. The RfD was set at 0.005 mg/kg/day, using a LEL of 0.5 mg/kg/day derived from a controlled human volunteer study. The study is cited as "Union Carbide Agricultural Products Company, Inc. 1977a. MRID 00066931." In that study, 10 humans were orally dosed at the 0.5 level for 16 days, followed by a recovery period of 29 days. The UF was set at 100 due to lack of a NOEL (i.e., 10x for lack of a NOEL, plus 10x for intra-species variability). The RfD determination also took into account as a non-principal study a human volunteer study ("Union Carbide, 1972) in which both males and females were given 1.8 mg/kg/day and a NOEL was not observed.

7. Ethion

Ethion is an organophosphate pesticide. EPA's online IRIS database shows that its oral RfD was last revised 09/01/1989. A NOEL of 0.05, and a LEL of 0.075, for plasma cholinesterase inhibition were based on a 21-day human volunteer study of 10 adult males. (Cited as FMC Corporation. 1970. MRID No. 00073157.) The RfD was also based on a subchronic (90-day) animal (dog) study showing inhibition of brain cholinesterase as a critical endpoint, with a NOEL of 0.06 mg/kg/day and a LEL of 0.71 mg/kg/day. An UF of 10 was used to account for intra-species variability in connection with the human data; and another 10x UF was added to account for the brain cholinesterase inhibition observed in the dog study. The RfD was set at 0.0005 mg/kg/day.

EPA issued a revised Human Health Risk Assessment for ethion on July 14, 1999. The revised risk assessment relied principally on animal studies, and the result was that the acute RfD was raised to 0.0017, while the chronic RfD remained at 0.0005. At 3. The risk assessment contains the following statement regarding the use of human test data:

> On July 27, 1998 the Agency announced that it is deeply concerned about the conduct of pesticide health effects [sic] on human subjects and that it would be consulting with its independent Science Advisory Board (SAB) about the application of stringent ethical standards to any such studies. The Agency further stated that no human studies of this type have been used by EPA for any final decisions about acceptable levels of pesticide under the new food safety law. Agency officials have stated that no final agency regulatory determinations will be based on this kind of human study until the Agency has in place an approach

for consideration of the ethical acceptability of any such study. At this time, the Agency has not yet received the response to its consultation with its scientific advisory committees and is continuing to work on its approach to these critical ethical questions.

During this period, EPA has continued to work through its risk assessment revisions and refinements for the organophosphates, including ethion, pursuant to the pilot process for public participation in risk assessment and risk management.

In previous assessments, reported in the Health Effects Division's Toxicity Endpoint Selection (TES) documents dated March 14, 1994 and October 10, 1995, the TES Committee based acute and chronic reference doses (RfDs), as well as occupational exposure and risk assessments, for ethion on a 21-day study conducted on human volunteers (MRID 00073157).

In light of the developing Agency policy on use of toxicology studies employing human subjects, and pending reassessment of this and other human studies for consideration of the ethical acceptability of such studies, HED has reconsidered the toxicology database for ethion and has for the acute dietary risk assessments, used a toxicology endpoint from an animal study and applied uncertainty factors informed by the existence of the human studies.

The standard uncertainty factor of 10 to account for interspecies extrapolation was reduced to 3. The intraspecies uncertainty factor of 10 was not reduced. Based on the NOAEL of 0.05 mg/kg/day established in an animal study, the acute dietary risk estimates do not exceed the Agency's level of concern for all populations, regardless of which interspecies factor was used (i.e., either 3 or 10).

All other risk assessments used only animal endpoints. OPP expects to reevaluate this acute dietary analysis pursuant to the Agency's decisions about how to consider the ethical acceptability of human studies and in light of the on-going efforts to develop peer-reviewed guidance for the scientific evaluation of any human studies that are determined to be ethically-appropriate for consideration in pesticide risk assessments.

At 2-3.

8. Malathion

The IRIS database shows that the oral RfD was last revised on 01/01/1992. At that time, the "principal study" supporting the RfD was a subchronic human volunteer feeding study, cited as "Moeller, H.C. and J.A. Rider, 1962. Plasma and red blood cell cholinesterase activity as indication of the threshold of incipient toxicity of ethyl-p-netrophenyl thiononobenzenephosphorate (EPN) and malathion in human beings. Toxicol. Appl. Pharmacol. 4:123-30." The study involved administering the chemical in gelatin capsules to five healthy adult male volunteers for 32, 47, and 56 days at various doses. The study determined a NOEL of

0.23 mg/kg/day. and a LEL of 0.34 for RBC ChE depression. An uncertainty factor of 10 was used to arrive at the RfD of 0.02 mg/kg/day.

Malathion is currently undergoing a new review in connection with the FQPA review of organophosphates. Available materials are not clear on whether the human volunteer study previously regarded as the principal study is being considered; however, there are indications that it is not. A Dec. 22, 1998 memorandum, entitled "Malathion – Re-Evaluation", by the Health Effects Division's Hazard Identification Review Committee states in one place: "The HIARC concluded that even if the human study (where no females were used) had been chosen as the basis for the RfD, it would not be appropriate to apply additional uncertainty factor [sic] to account for the increased sensitivity of females as compared to males." At 16, underlining as in original.

9. Mercury and mercury compounds

EPA's IRIS oral RfD for methylmercury was last revised on 07/27/2001. Instead of employing a LOAEL/NOAEL approach, the RfD is based on a Benchmark Dose approach (BMD), with a "critical effect" of developmental neuropsychological impairment. While the "principal study" cited is a Faroe Islands epidemiologic study, employment of the BMD approach necessarily required dose conversion data, including data on human absorption, distribution, and excretion, and for these types of necessary data the Agency relied on at least five controlled human volunteer studies involving ingestion of fish contaminated with specific quantities of methymercury.

The methylmercury RfD summary shows that it relied substantially for its data on the Agency's mandated 1997 Mercury Study Report to Congress. (EPA-452/R-97-007, Dec. 1997.) That study also shows that substantial reliance was place on human volunteer studies for determining absorption and elimination rates in humans of elemental mercury, inorganic mercury, and methylmercury. *Id* at 2-1, 2-2, 2-3, 2-7, 2-8, 2-13, 2-14, 6-23, 6-24, 6-48, B-38, B-39 and B-43.

In January 2000, EPA issued final "Water Quality Criterion for the Protection of Human Health: Methylmercury". (EPA-823-R-01-001, Jan. 2001.) The criterion is not a binding regulation, but is intended to provide guidance to States and Tribes in setting water quality standards. (66 Fed.Reg. 1344 et seq., Jan. 8, 2001.) The criterion document states that it relies primarily on the information contained in the 1997 report to Congress, and briefly summarizes several human volunteer studies which provided human oral absorption and distribution data. *Id.* at 2-1 and 2-2.

10. Methyl parathion

The IRIS oral RfD was last revised 03/01/91. The RfD was based on a NOEL of 0.025 mg/kg/day observed in a 2-yr. rat feeding study. An uncertainty factor of 100 was applied to reach an RfD of 0.00025 mg/kg/day. Although treated as a "principal study", this rat feeding study was classified as only "supplementary". The portion of the RfD Summary under "Additional Studies/Comments" contains the following explanation regarding a human volunteer study for which only an abstract was available:

> In a subchronic study (30 days) with methylparathion in humans (Rider et al., 1971), RBC cholinesterase depression was reported, with a NOEL of approximately 0.3 mg/kg/day. Using a UF of 100 to adjust for chronic exposure and intraspecies sensitivity, an RfD based on this study would be 0.003 mg/kg/day. Adequate supporting data for human studies are not available. Nevertheless, even anecdotal data directly relating to human exposure should not be dismissed. Therefore, an RfD based on animal studies should not exceed 0.003 mg/kg/day unless additional data for humans can be found to support such a determination.

11. Nitrogen dioxide

EPA published a final rule on October 8, 1996 determining not to change the existing national ambient air quality standards for nitrogen dioxide. 61 Fed.Reg. 52852 et seq. The final rule relied on the health effects assessment presented in the Oct. 11, 1995 notice of proposed rulemaking. 60 Fed.Reg.52874 et seq. The standards decision relied substantially on human volunteer clinical studies of asthmatics (including adolescent asthmatics) for changes, and absence or reversibility of health effects, in pulmonary function or airway responsiveness. 60 Fed.Reg. at 52878, 52879 3d col. Additional information supporting the decision was presented in the 1993 "Air Quality Criteria for Oxides of Nitrogen" (EPA/600/8-91/049aF, Aug. 1993). The controlled human volunteer studies were discussed at 1-19 (Executive Summary), Chapter 15 (pp. 15-1 to 15-105 ("Controlled Human Exposure Studies of Nitrogen Oxides"), and Chapter 16, pp. 16-1 to 16-2 ("Health Effects Associated with Exposure to Nitrogen Dioxide", referring back to Chapter 15). The OAQPS Staff Paper supporting the decision not to revise the standard contains extensive discussion of the findings from the controlled human volunteer studies assessed in the Criteria Document. "Review of the National Ambient Air Quality Standards for Nitrogen Dioxide – Assessment of Scientific and Technical Information", pp. vii-viii, 16, 33-38, 43-46, 49-50, EPA-452/R-95-005, Sept. 1995.

12. Ozone

On July 18, 1997, EPA issued a final rule containing its decision to revise the national ambient air quality standard (NAAQS) for ozone and replace the 1-hr. standard with an 8-hr. standard. 62 Fed.Reg. 38856 *et seq.* The decision was based substantially on controlled human

studies of healthy and asthmatic subjects for lung function decrements, respiratory symptoms (e.g., cough, pain on deep inspiration), non-specific bronchial responsiveness, biochemical indicators of pulmonary inflammation, and exercise response. *Id.* at 38863-64, 38872, and 38873 and Criteria Document. Most, if not all, of the studies relied on were conducted by EPA. *Id.* at 38867. See also the Criteria Document at 1-23 to 1-26 (Executive Summary).

13. Pirimiphos-methyl

The IRIS database shows that the oral RfD was last revised 01/01/1992. The principal studies supporting the RfD are two human volunteer feeding studies. One is a 56-day study with three males and four females, cited as ICI Americas Inc. 1976a. MRID No. 00080732; HED Doc. No. 005105. The other is 28-day feeding study with five males, cited as ICI Americas Inc. 1974a. MRID No. 00080747; HED Doc. No. 005105.

14. Sulphur dioxide

On May 22, 1996, EPA published a final decision not to revise the NAAQS for sulphur oxides. 61 Fed.Reg. 25566. The decision relies substantially on controlled human volunteer studies of mild, moderate, and moderate/severe asthmatic subjects exposed via mouthpiece or in chamber. Id. at 25570-73. Those studies are discussed in detail and evaluated in the *Supplement to the Second Addendum (1986) to Air Quality Criteria for Particulate Matter and Sulfur Oxides (1982): Assessment of New Findings on Sulfur Dioxide Acute Exposure Health Effects in Asthmatic Individuals (1994)*(EPA-600/FP-93/002).

15. Zinc and zinc compounds (soluble salts)

The IRIS database shows that the oral RfD was last revised on 10/01/92. The RfD was based on a human clinical study which investigated the effects of oral zinc supplements on copper and iron balance in 18 healthy women over 10 weeks. (Yadrick et al., 1989.) The effects on copper and iron biochemistry are stated to be a concern because long-term iron or copper deficiency could result in significant adverse effects--for example, anemia and increased risk of coronary artery disease. The study found a LOAEL of 1.0 mg/kg/day, and did not determine a NOAEL. An uncertainty factor of 3 was used to arrive at an RfD of 0.3 mg/kg/day.

States Environmental
ion Agency

NHEERL

Dedication Media

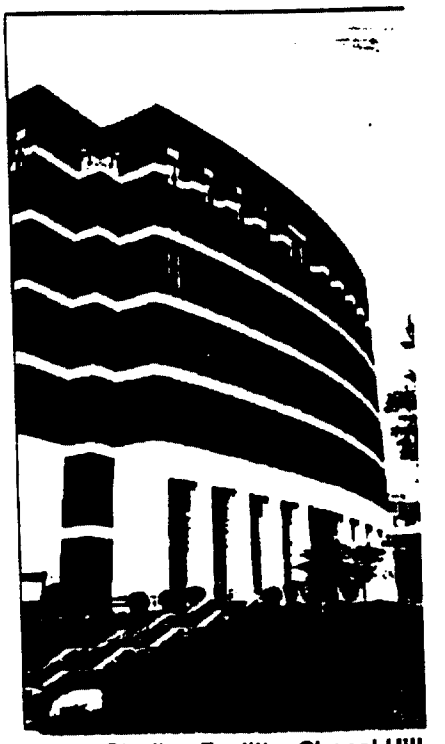
INHALATION CHAMBERS

DIRECTIONS

Air Pollution Inhalation Chambers Dedicated for Human Health Research

Print V

Research Triangle Park, NC....The U.S. Environmental Protection Agency's Office of Research and Development will hold a dedication ceremony at its Human Studies Facility in Chapel Hill, North Carolina, on Tuesday, Nov. 14, from 9 a.m. to 11 a.m. to mark the completion and availability of eight state-of-the-art **inhalation chambers**.



Human Studies Facility, Chapel Hill,

The research facility houses the EPA's Human Studies Division of the National Health and Environmental Effects Research Laboratory. The **inhalation chambers** represent state-of-the-art technology for conducting studies to advance the science of the human health effects of air pollutants.

"This dedication will unveil the Human Studies Facility as a national resource for human health research," says Dr. Hillel Koren, Director of EPA's Human Studies Division. "We are working to make these high-tech research tools available to other scientists."

The eight human **inhalation chambers** and *in vitro* (cell culture) exposure **ch** are shared by **EPA** and University of North Carolina scientists through a coo agreement. Because these **chambers** are such unique research tools, the **ch** will also be made available to outside scientists conducting air pollution resea

other areas of environmental health in the public interest.

HSD scientist monitors a volunteer using specialized equipment in a controlled exposure study.

The dedication ceremony will be atte national and international sc representatives from research ins and local, state, and regional dignitar Keynote Speaker for the de ceremony will be Dr. Norine Assistant Administrator for the EPA of Research and Development. Othe speakers are: Congressman David P Lawrence Reiter, Director of the Health and Environmental Effects R Laboratory; Dr. Jeffrey Houpt, Dean o School of Medicine; Dr. Thomas Deputy Director of EPA's Office of Air Quality Planning & Standards; and Dr. Glaze, Director of the Carolina Environmental Program at UNC.

As part of the celebration, the EPA will sponsor a Symposium by invitation "Air Pollution and Public Health in the 21st Century" from 1:30 p.m. - 4:00 p.m Seminar Room at the Chapel Hill facility. The symposium will featu internationally-renowned experts who will discuss the role of health-effects r in assessing the risks air pollutants may pose to humans.

Note to Editors: A media tour of the Human Studies Facility and int chambers is available at 11 a.m. following the ceremony. The media invited to attend the Symposium. To participate in a tour or atte Symposium, please contact Ann Brown at 919-541-7818 or by cellular tel the day of the event at 919-605-5827.

EPA Home | ORD Home | NHEERL Home | Search EPA | Search NHEERL | EPA People Lo

An Up-Close Look at EPA's Human Inhalation Chambers

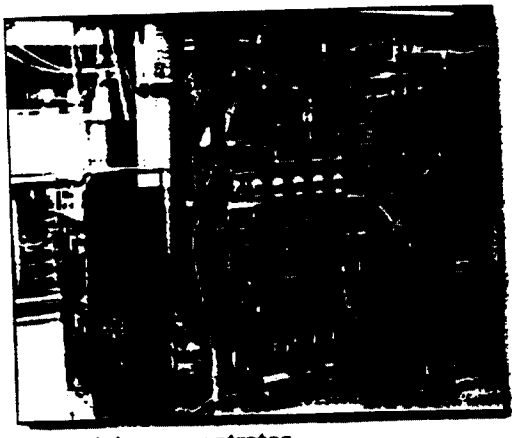
A special three-story wing in the U.S. Environmental Protection Agency's Human Studies Facility in Chapel Hill, NC, houses state-of-the-art inhalation chambers used to conduct controlled clinical studies as part of the EPA's mission to protect the public health from pollutants. The eight chambers -- which vary in size, design and capabilities -- are high-tech research tools furnished with specialized equipment for generating and measuring a wide range of pollutants, including gases, volatile organic compounds, particles, and water soluable aerosols.

Exposure chambers fitted with exer equipment.

"These state-of-the-art controlled human exposure systems offer unparalleled precision and versatility, and represent an important milestone in the advancement of environmental science and public health," says Dr. Lawrence W. Reiter, Director of the National Health and Environmental Effects Research Laboratory in Research Triangle Park, NC.

Using the chambers, scientists can study the health effects of components th up smog that many Americans are exposed to every day in large metropolita such as Los Angeles or Houston. Previous studies on humans have cor significantly to the understanding of the health effects of ozone that led development of the current ozone standards.

The EPA is a leader in developing the technology that has made the e chambers possible. The chambers require high-tech equipment to prepare air. The first step in the process is to purify the air to ensure that any effects o in exposed volunteers are due only to the specific air pollutants under stu purification process occurs on the top floor of the special wing, where three foot custom-designed air cleaning units, remove almost all of the pollutants, moisture. Each of the units can supply 5,500 cubic feet of clean air per minu inhalation chamber -- the same amount of air it takes to fill approximately 7,3 balloons.



Air particle concentrator.

Once cleaned, the air flows dedicated air handlers which design" the air stream by controlling rate, temperature and humid accordance with the study design. then undergoes a final filtering to any remaining particles, includin pollens, and smoke particles as sm bacterium (0.3 microns). Finally, p measured amounts of pollutants s ozone, are injected into the conditic stream as it enters the exposure cha

"The health effects of certain air p can vary depending on the atmospheric conditions, whether its humid or dry, hot or cool, windy or calm," Dr. Hillel Koren, Director of the Human Studies Division in Chapel Hill. chambers offer us unique opportunities to produce air that can be found anywhere in the United States."

The two largest chambers have 295 square-feet of space each and offer t versatility for testing, with a temperature range of 45 to 95 degrees F and from bone dry to 75 percent humidity. These stainless steel units are the only their kind in the United States and are the cornerstone of the research facility's air pollution studies. They can accommodate several subjects over several d are equipped with bathrooms. Subjects are constantly monitored, and can ea and undergo a battery of tests during their stay. Lung function, heart monitor in some cases, cognitive function are among the measurements taken during to assess physiological effects and to ensure the subjects' safety.

Smaller chambers and a host of other specially-designed chambers for in exposure to specific pollutants round out the complement of exposure capabilities at the facility. In addition, the Human Studies Facility includes equipped and staffed medical station to support the clinical research activities at EPA and the University of North Carolina's Center for Environmental Medic Lung Biology.

EPA Home | ORD Home | NHEERL Home | Search EPA | Search NHEERL | EPA People Loc

This page is located at: http://www.epa.gov/nheerl/dedication/hsdchambers.html
This page last updated: June 20, 2001

Eastern Resource Center
Federal Highway Administration
10 S. Howard Street, Suite 4000
Baltimore, MD 21201

Air Quality Update

December 4, 2000

MOBILE6 USER GUIDE AVAILABLE

Just over a month prior to the model's expected release, EPA has announced the release of the draft user guide for the MOBILE6 emissions model. The draft has been produced by the agency's Office of Transportation and Air Quality (OTAQ).

A lengthy 150 pages, the new model's documentation includes a detailed description of the various inputs required to run this latest version of EPA's MOBILE series of models. EPA still projects a January release for MOBILE6 which has been in active development over the past four years.

In addition to a rundown on the inputs necessary to operate the model, the guidance also describes the outputs available with the new model. EPA officials caution that the users guide is a draft and changes should be expected in the final product. The agency recommends that interested parties download the guide at the MOBILE6 website: www.epa.gov/otaq/m6.htm.

Meanwhile, EPA's OTAQ developers report that the basic coding of the model has been completed and pilot testing has commenced. The bottom line for state and local users of the new MOBILE6 model? Pending successful testing of the draft model, OTAQ is anticipating an official release of MOBILE6 in late January, 2001. A grace period for states and local transportation and air quality agencies to use the model will be published shortly thereafter in the Federal Register.

BILL WOULD SUSPEND STANDARDS DURING EPISODES, EVENTS

A host of possible proposed changes to the Clean Air Act may include one that could change substantially the impacts of extreme pollution events, such as ozone episodes.

One senator active in environmental matters is set to introduce an amendment to the Act that would ignore air quality violations generated by such "unusual events."

Oklahoma Sen. James Inhofe (R), chairman of the Environment and Public Works, Clean Air Subcommittee has developed several proposed amendments to the CAA and hopes to ignite debate in the Senate over reauthorization of the Act during the next Congress. The bill dealing with air pollution events would effectively suspend air standards during such situations. The draft legislation establishes a definition for such exceptional events as any "unusual or other event" not reasonably controlled through a State Implementation Plan such as a "forest fire, volcanic activity, a dust storm, or an unusual meteorological condition."

While such unusual, exceptional events have been defined by the more populous areas of the country as ozone episodes tied to hot, summer weather, the impetus for Inhofe's potential legislation is tied to wildfires in the West and Southwest. Oklahoma state officials have been pleading their case with EPA that recent high pollution measurements can be linked to the summer's devastating forest and wild fires and that such events are well beyond their control as air regulators.

EPA officials have countered that the agency already grants waivers for some unusual or exceptional events, and that no change in policy or law is necessary. Howeve, Oklahoma regulators claim that the burden of proof still rests with the states and involves an unduly burdensome process.

Inhofe's bill on unusual events has not been introduced, nor have others aimed at amendment of the CAA. Congressional observers suspect, however, that it may be brought to the floor soon after opening of the next session.

ADVANCED AIR CHAMBERS USED IN NC RESEARCH

Health effects and other researchers have launched into a new dimension of air quality study at EPA's Office of Research and Development in Chapel Hill, North Carolina. Dedicated last month, a program employing advanced inhalation chambers has been implemented by scientists from both EPA and the University of North Carolina.

The eight inhalation chambers will be used to measure the human impacts of various levels of harmful air pollutants. The chambers engage human volunteers and vary in size, design, and capabilities. While each chamber is unique in its technical advancements and sensitivity, all eight are identified as advanced research tools. The specialized equipment involved will allow researchers to generate and measure an assortment of pollutants, including volatile organic compounds (VOCs), fine particles, and aerosols.

Researchers point out that the initial stage in the process will be to purify the chambers' air to ensure a causal relationship can be demonstrated with any specific pollutant added to the test. Established rates of pollutants, such as ozone or VOCs, are then introduced to the volunteers through the chamber's air stream. Effects on the subjects will be monitored during a normal regimen of activities, as they can eat, sleep, or undergo specific tests during their stay. Researchers participating in the program note that the results of the testing could be used in developing new air quality standards. (MK-261)

Previous AQ Updates

Contact Mike Koontz with questions and comments on the Air Quality update.

Contact ERC

Last updated January 16, 2001

Issue Sections

Data Access

Data Quality

Regulation by Litigation

Regulation by Information

Regulation by Appropriation

Special Projects

CRE Watch List

Emerging Regulatory Issues

Litigation

OMB Papers

Abstracts and Reviews of New Papers

Guest Column

Services

Regulatory Review & Representation

Voluntary Standards Program

CRE Report Card

Public Docket Preparation

Interactive Public Docket

Electronic Regulatory Forum

Consumer Response Service

Site Search

Enter keyword(s) to search TheCre.com:

Guest Columnists

Weidenbaum Center to Sponsor Forum on OMB's Executive Regulatory Review

On December 17, 2001, the Weidenbaum Center on the Economy, Government, and Public Policy of the Washington University in St. Louis will host a forum on OMB's Executive Regulatory Review at the National Press Club in Washington, D.C. Among its speakers, the meeting will feature a number of current and former officials from OMB's Office of Information and Regulatory Affairs.

The meeting is entitled "Executive Regulatory Review: Surveying the Record, Making it Work," and the forum is expected to generate lively debate on a range of volatile regulatory issues. The first session will involve a history of executive regulatory review, and the second session will explore how the regulatory review process can work effectively.

The forum will be held from 7:30 a.m. until 2:00 p.m., and its is free and open to the public. However, space is limited, so persons interested in attending should contact the Center's Melinda Warren via e-mail (warren@wc.wustl.edu) or by phone at (314) 935-5652.

- Click here to review the forum agenda and to obtain registration information. (pdf 12kb)

Search